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Association Between Telomere Length and Risk of Cancer and Non-Neoplastic Diseases

Citation for published version:

The Telomeres Mendelian Randomization Collaboration, Haycock, PC, Burgess, S, Nounu, A, Zheng, J, Okoli, GN, Bowden, J, Wade, KH, Timpson, NJ, Evans, DM, Willeit, P, Aviv, A, Gaunt, TR, Hemani, G, Mangino, M, Ellis, HP, Kurian, KM, Pooley, KA, Eeles, RA, Lee, JE, Fang, S, Chen, WV, Law, MH, Bowdler, LM, Iles, MM, Yang, Q, Worrall, BB, Markus, HS, Hung, RJ, Amos, CI, Spurdle, AB, Thompson, DJ, O'Mara, TA, Wolpin, B, Amundadottir, L, Stolzenberg-Solomon, R, Trichopoulou, A, Onland-Moret, NC, Lund, E, Duell, EJ, Canzian, F, Severi, G, Overvad, K, Gunter, MJ, Tumino, R, Svenson, U, van Rij, A, Baas, AF, Bown, MJ, Albagha, O & Ralston, SH 2017, 'Association Between Telomere Length and Risk of Cancer and Non-Neoplastic Diseases: A Mendelian Randomization Study', *JAMA Oncology*, vol. 3, no. 5, pp. 636-651. <https://doi.org/10.1001/jamaoncol.2016.5945>

Digital Object Identifier (DOI):

[10.1001/jamaoncol.2016.5945](https://doi.org/10.1001/jamaoncol.2016.5945)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

JAMA Oncology

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1 **Mendelian randomization study of the association between telomere length and risk of**
2 **cancer and non-neoplastic diseases**

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16 2995 words [word limit 3000]

17 3 figures, 2 tables, 132 references; 7 supplementary figures / 6 supplementary tables

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26 **ABSTRACT 349 WORDS**

27 **Importance** The causal direction and magnitude of the association between telomere length
28 and incidence of cancer and non-neoplastic diseases is uncertain, due to the susceptibility of
29 observational studies to confounding and reverse causation.

30 **Objective** To conduct a Mendelian randomization study, using germline genetic variants as
31 instrumental variables, to appraise the causal relevance of telomere length for risk of cancer
32 and non-neoplastic diseases.

33 **Data Sources** Genome-wide association studies (GWAS) published up to January 15 2015.

34 **Study Selection** GWAS of non-communicable diseases that assayed germline genetic
35 variation and did not select cohort or control participants on the basis of pre-existing diseases.
36 Of 163 GWAS of non-communicable diseases identified, summary data from 103 were
37 available.

38 **Data Extraction** Summary association statistics for single nucleotide polymorphisms (SNPs)
39 that are strongly associated with telomere length in the general population.

40 **Main Outcomes** Odds ratios (ORs) for disease per standard deviation (SD) higher telomere
41 length due to germline genetic variation.

42 **Results** Summary data were available for 35 cancers and 48 non-neoplastic diseases,
43 corresponding to 420,081 cases (median 2,526 per disease) and 1,093,105 controls (median
44 6,789 per disease). Increased telomere length due to germline genetic variation was generally
45 associated with increased risk for site-specific cancers. The strongest associations were
46 observed for (ORs per 1-SD change in genetically increased telomere length): glioma 5.27
47 (3.15-8.81), serous low-malignant-potential ovarian cancer 4.35 (2.39-7.94), lung
48 adenocarcinoma 3.19 (2.40-4.22), neuroblastoma 2.98 (1.92-4.62), bladder cancer 2.19 (1.32-
49 3.66), melanoma 1.87 (1.55-2.26), testicular cancer 1.76 (1.02-3.04), kidney cancer 1.55

50 (1.08-2.23) and endometrial cancer 1.31 (1.07-1.61). Associations were stronger for rarer
51 cancers and at tissue sites with lower rates of stem cell division ($P < 0.05$). There was
52 generally little evidence of association between genetically increased telomere length and risk
53 of psychiatric, autoimmune, inflammatory, diabetic and other non-neoplastic diseases, except
54 for coronary heart disease (0.78 [0.67-0.90]), abdominal aortic aneurysm (0.63 [0.49-0.81]),
55 celiac disease (0.42 [0.28-0.61]) and interstitial lung disease (0.09 [0.05- 0.15]).

56 **Conclusions** It is likely that longer telomeres increase risk for several cancers but reduce risk
57 for some non-neoplastic diseases, including cardiovascular diseases.

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71 INTRODUCTION

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73 At the ends of chromosomes, telomeres are DNA-protein structures that protect the genome
74 from damage, shorten progressively over time in most somatic tissues¹ and are proposed
75 physiological markers of ageing.^{2,3} Shorter leukocyte telomeres are correlated with older age,
76 male sex and other known risk factors for non-communicable diseases⁴⁻⁶ and are generally
77 associated with higher risk for cardiovascular diseases^{7,8}, type 2 diabetes⁹ and non-vascular
78 non-neoplastic causes of mortality.⁸ Whether these associations are causal, however, is
79 unknown. Telomere length has also been implicated in risk of cancer but the direction and
80 magnitude of the association is uncertain and contradictory across observational studies.¹⁰⁻¹⁴
81 The uncertainty reflects the considerable difficulty of designing observational studies of
82 telomere length and cancer incidence that are robust to reverse causation, confounding and
83 measurement error.

84 The aim of the present report was to conduct a Mendelian randomization study, using
85 germline genetic variants as instrumental variables for telomere length, to help clarify the
86 nature of the association between telomere length and risk of cancer and non-neoplastic
87 diseases. The approach, which mimics the random allocation of individuals to the placebo
88 and intervention arms of a randomized controlled trial, allowed us to: (1) estimate the
89 direction and broad magnitude of the association of telomere length with risk of multiple
90 cancer and non-neoplastic diseases; (2) appraise the evidence for causality in the estimated
91 etiological associations; (3) investigate potential sources of heterogeneity in findings for site-
92 specific cancers; and (4) compare genetic estimates to findings based on directly measured
93 telomere length in prospective observational studies.

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95 **METHODS**

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97 *Study design*

98 The design of our study, illustrated in Figure S1, had three key components: 1) the
99 identification of genetic variants to serve as instruments for telomere length; 2) the
100 acquisition of summary data for the genetic instruments from genome wide association
101 studies (GWASs) of diseases and risk factors for non-communicable diseases; and 3) the
102 classification of diseases and risk factors into primary or secondary outcomes based on *a*
103 *priori* statistical power. As a first step, we searched the GWAS catalog^{15,16} on the 15 January
104 2015, to identify single nucleotide polymorphisms (SNPs) associated with telomere length.
105 To supplement the list with additional potential instruments, we also searched the original
106 study reports curated by the GWAS catalog (using a P-value threshold of 5×10^{-8}).¹⁷⁻²⁵ We
107 acquired summary data for all SNPs identified by our search from a meta-analysis of GWASs
108 of telomere length, involving 9,190 participants of European ancestry.¹⁸

109 The second key component of our design strategy involved the acquisition of summary data,
110 corresponding to the selected genetic instruments for telomere length, from GWASs of non-
111 communicable diseases and risk factors (Fig. S1). As part of this step, we invited principal
112 investigators of non-communicable disease studies curated by the GWAS catalog^{15,26} to share
113 summary data for our study (see Fig. S1 for further details). We also downloaded summary
114 data for diseases and risk factors from publically available sources, including study-specific
115 websites, dbGAP, ImmunoBase and the GWAS catalog (Fig. S1).

116 The third key component of our design strategy was the classification of diseases and risk
117 factors into either primary or secondary outcomes, which we defined on the basis of *a priori*
118 statistical power to detect associations with telomere length. Primary outcomes were defined

as diseases with sufficient cases and controls for >50% statistical power and secondary outcomes defined as diseases with <50% statistical power to detect odds ratios ≥ 2.0 per standard deviation (SD) change in genetically increased telomere length (alpha assumed to be 0.01). All risk factors were defined as secondary outcomes. Risk factors with <50% statistical power were excluded.

Further details on our design strategy can be found in the supplement.

Comparison with prospective observational studies

We searched PubMed for prospective observational studies of the association between telomere length and disease (see Tables S3 and S4 for details of the search strategy and inclusion criteria). Study-specific relative risks for disease per unit change or quantile comparison of telomere length were transformed to a SD scale using previously described methods.²⁷ Hazard ratios, risk ratios and odds ratios were assumed to approximate the same measure of relative risk. Where multiple independent studies of the same disease were identified, these were combined by fixed effects meta-analysis, unless there was strong evidence of between-study heterogeneity ($P_{\text{Cochran's } Q} < 0.001$), in which case they were kept separate.

Statistical analysis

We combined summary data across SNPs into a single instrument, using maximum likelihood to estimate the slope of the relationship between β_{GD} and β_{GP} and a variance-covariance matrix to make allowance for linkage disequilibrium between SNPs,²⁸ where β_{GD} is the change in disease log odds or risk factor levels per copy of the effect allele and β_{GP} is the SD change in telomere length per copy of the effect allele (see supplementary methods

for technical details). The slope from this approach can be interpreted as the log odds ratio for binary outcomes, or the unit change for continuous risk factors, per SD change in genetically increased telomere length. P-values for heterogeneity amongst SNPs, in the estimated associations of genetically increased telomere length with disease and risk factors, were estimated by likelihood ratio tests.²⁸ Associations between genetically increased telomere length and continuous risk factors were transformed into SD units. For five secondary disease outcomes where only a single SNP was available for analysis, we estimated associations using the Wald ratio: β_{GD}/β_{GP} , with standard errors approximated by the delta method.²⁹

Inference of causality in the estimated etiological associations between telomere length and disease depends on satisfaction of Mendelian randomization assumptions (Fig. S7; see Table S6 for a glossary of terms).^{30,31} The assumptions are: 1) the selected SNPs are associated with telomere length; 2) the selected SNPs are not associated with confounders; and 3) the selected SNPs are associated with disease exclusively through their effect on telomere length. If these assumptions are satisfied, the selected SNPs are valid instrumental variables and their association with disease can be interpreted as a causal effect of telomere length. We modeled the impact of violations of these assumptions through two sets of sensitivity analyses: a weighted median function³² and MR-Egger regression³⁰ (see supplementary methods for technical details). We restricted our sensitivity analyses to diseases showing the strongest evidence of association with genetically increased telomere length (defined as $P_{\text{Bonferroni}} \leq 0.05$).

We used meta-regression to appraise potential sources of heterogeneity in our findings for cancer. The association of genetically increased telomere length with the log odds of cancer was regressed on cancer incidence, survival time and median age-at-diagnosis, downloaded from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER)

Program,³³ and tissue-specific rates of stem cell division from Tomasetti and Vogelstein.³⁴ As the downloaded cancer characteristics from SEER correspond to the United States population, 77% of which was of white ancestry in 2015³⁵, the meta-regression analyses excluded genetic studies conducted in East Asian populations.

All analyses were performed in R version 3.1.2³⁶ and Stata release 13.1 (StataCorp, College Station, TX). P-values were two-sided and evidence of association was declared at $P < 0.05$. Where indicated, Bonferroni corrections were used to make allowance for multiple testing, although this is likely to be overly conservative given the non-independence of many of the outcomes tested.

RESULTS

We selected 16 SNPs as instruments for telomere length (Fig. S1 & Table 1). The selected SNPs correspond to 10 independent genomic regions that collectively account for 2-3% of the variance in leukocyte telomere length, which is equivalent to an F statistic of ~ 18 . This indicates that the genetic instrument, constructed from these 10 independent genomic regions, is strongly associated with telomere length (details in supplementary discussion).³⁷ Summary data for the genetic instruments were available for 83 non-communicable diseases, corresponding to 420,081 cases (median 2,526 per disease) and 1,093,105 controls (median 6,789 per disease), and 44 risk factors (Fig. S1, Table 2 and Table S1). The median number of SNPs available across diseases was 11 (min=1, max=13) and across risk factors was 12 (min=11, max=13). Of the 83 diseases, 56 were classified as primary outcomes and 27 as secondary outcomes (Table 2, Fig. S1 and Table S1). For 9 of the 83 non-communicable diseases, additional summary data were available from 10 independent studies for replication

analyses, corresponding to 40,465 cases (median 1,416 per disease) and 52,306 controls (median 3,537 per disease) (Table S1).

The results from primary analyses of non-communicable diseases are presented in Figure 1; results from secondary analyses of risk factors and diseases with low *a priori* power are presented in the supplement (Fig. S2, S5 and S6). Genetically increased telomere length was associated with higher odds of disease for 9 of 22 primary cancers ($P < 0.05$), including (odds ratio [95% confidence interval]): glioma (5.27 [3.15-8.81]), endometrial cancer (1.31 [1.07-1.61]), kidney cancer (1.55 [1.08-2.23]), testicular germ cell cancer (1.76 [1.02-3.04]), melanoma (1.87 [1.55-2.26]), bladder cancer (2.19 [1.32-3.66]), neuroblastoma (2.98 [1.92-4.62]), lung adenocarcinoma (3.19 [2.40-4.22]) and serous low-malignancy-potential (LMP) ovarian cancer (4.35 [2.39-7.94]) (Fig. 1). The associations were, however, highly variable across cancer types, varying from an odds ratio of 0.86 (0.50-1.48) for head and neck cancer to 5.27 (3.15-8.81) for glioma. Substantial variability was also observed within tissue sites. For example, the odds ratio for lung adenocarcinoma was 3.19 (2.40-4.22) compared to 1.07 (0.82-1.39) for squamous cell lung cancer. For serous LMP ovarian cancer the odds ratio was 4.35 (2.39-7.94) compared to odds ratios of 1.21 (0.87-1.68) for endometrioid ovarian cancer, 1.12 (0.94-1.34) for serous invasive ovarian cancer, 1.04 (0.66-1.63) for clear cell ovarian cancer and 1.04 (0.73-1.47) for mucinous ovarian cancer. The strongest evidence of association was observed for glioma, lung adenocarcinoma, neuroblastoma and serous LMP ovarian cancer ($P_{\text{Bonferroni}} < 0.05$). Results for glioma and bladder cancer showed evidence for replication in independent datasets (independent datasets were not available for other cancers) (Fig. S3).

Genetically increased telomere length was associated with reduced odds of disease for 6 of 32 primary non-neoplastic diseases ($P < 0.05$), including coronary heart disease (0.78 [0.67-0.9]), abdominal aortic aneurysm (0.63 [0.49-0.81]), Alzheimer's disease (0.84 [0.71-0.98]), celiac

disease (0.42 [0.28-0.61]), interstitial lung disease (0.09 [0.05-0.15]) and type 1 diabetes (0.71 [0.51-0.98]) ($P < 0.05$) (Figure 1). The strongest evidence of association was observed for coronary heart disease ($P_{\text{Bonferroni}} = 0.05$) and abdominal aortic aneurysm, celiac disease and interstitial lung disease ($P_{\text{Bonferroni}} < 0.05$). The associations with coronary heart disease and interstitial lung disease showed evidence for replication in independent datasets (Fig. S3).

Our genetic findings were generally similar in direction and magnitude to estimates based on observational prospective studies of leukocyte telomere length and disease (Figure 3). Our genetic estimates for lung adenocarcinoma, melanoma, kidney cancer and glioma, were, however, stronger in comparison to observational estimates.

In sensitivity analyses, we appraised the potential impact of confounding by pleiotropic pathways on our results. Associations estimated by the weighted median and MR-Egger were broadly similar to the main results for glioma, lung adenocarcinoma, serous LMP ovarian cancer, neuroblastoma, abdominal aortic aneurysm, coronary heart disease and interstitial lung disease (Fig. S4). In the second set of sensitivity analyses, implemented by MR-Egger regression, we found little evidence for the presence of pleiotropy ($P_{\text{intercept}} \geq 0.27$) (Fig. S4). The MR-Egger analyses were, however, generally underpowered, as reflected by the wide confidence intervals in the estimated odds ratios.

In meta-regression analyses, we observed that genetically increased telomere length tended to be more strongly associated with rarer cancers ($P = 0.02$) and cancers at tissue-sites with lower rates of stem cell division ($P = 0.02$) (Figure 2). The associations showed little evidence of varying by percentage survival five years after diagnosis or median age-at-diagnosis ($P \geq 37$).

DISCUSSION

In this report we show that genetically increased telomere length is associated with increased risk of several cancers and with reduced risk of some non-neoplastic diseases. Given the random distribution of genotypes in the general population with respect to lifestyle and other environmental factors, as well as the fixed nature of germline genotypes, these results should be less susceptible to confounding and reverse causation in comparison to observational studies. Our results are therefore compatible with causality. On the other hand, our results could reflect violations of Mendelian randomization assumptions, such as confounding by pleiotropy, population stratification or ancestry.³⁸ Although we cannot entirely rule out this possibility, the majority of our results persisted in sensitivity analyses that made allowance for violations of Mendelian randomization assumptions. Confounding by population stratification or ancestry is also unlikely, given the adjustments made for ancestry in the disease GWASs (see supplementary discussion).

Comparison with previous studies

Our findings for cancer are generally contradictory to those based on retrospective studies, which tend to report increased risk for cancer in individuals with shorter telomeres.^{11,12,39–42} The contradictory findings may reflect reverse causation in the retrospective studies, whereby shorter telomeres arise as a result of disease, or of confounding effects, e.g. due to cases being slightly older than controls even in age-matched analyses. Our findings for cancer are generally more consistent with those based on prospective observational studies, which tend to report weak or null associations of longer leukocyte telomeres with overall and site-specific risk of cancer,^{10–13,41,43–62} with some exceptions.⁶³ Our results are also similar to previously reported Mendelian randomization studies of telomere length and risk of

melanoma, lung cancer, chronic lymphocytic leukemia and glioma.⁶⁴⁻⁶⁷ The shape of the association with cancer may not, however, be linear over the entire telomere length distribution. For example, individuals with dyskeratosis congenita, a disease caused by germline loss-of-function mutations in the telomerase component genes *TERC* and *TERT*, have chronically short telomeres and are at increased risk of some cancers, particularly acute myeloid leukemia and squamous cell carcinomas arising at sites of leukoplakia,^{68,69} presumably due to increased susceptibility to genome instability and chromosomal end-to-end fusions.⁷⁰ Our results should therefore be interpreted as reflecting the average association at the population level and may not be generalizable to the extreme ends of the telomere length distribution.

Mechanisms of association

Our cancer findings are compatible with known biology.⁷⁰ By limiting the proliferative potential of cells, telomere shortening may serve as a tumour suppressor; and individuals with longer telomeres may be more likely to acquire somatic mutations owing to increased proliferative potential.⁷⁰ Rates of cell division are, however, highly variable amongst tissues³⁴ and thus the relative gain in cell proliferative potential, conferred by having longer telomeres, may also be highly variable across tissues. This could explain the ~6-fold variation in odds ratios observed across cancer types in the present study, as well as the tendency of our results to be stronger at tissue sites with lower rates of stem cell division. For example, the association was strongest for glioma (OR=5.27) and comparatively weak for colorectal cancer (OR=1.09) and the rates of stem cell division in the tissues giving rise to these cancers differ by several orders of magnitude. In neural stem cells, which give rise to gliomas, the number of divisions is ~270 million and for colorectal stem cells is ~1.2 trillion over the average lifetime of an individual.³⁴ The observation that genetically increased telomere

length was more strongly associated with rarer cancers potentially reflects the same mechanism, since rarer cancers also tend to show lower rates of stem cell division.³⁴ For example, the incidence of glioma is 0.4 and for colorectal cancer is 42.4 per 100,000 per year in the United States.³³

The inverse associations observed for some non-neoplastic diseases may reflect the impact of telomere shortening on tissue degeneration and an evolutionary trade-off for greater resistance to cancer at the cost of greater susceptibility to degenerative diseases, particularly cardiovascular diseases.^{71,72}

Study limitations

Our study is subject to some limitations, in addition to the Mendelian randomization assumptions already considered above. First, our method assumes that the magnitude of the association between SNPs and telomere length is consistent across tissues. Second, our study assumed a linear shape of association between telomere length and disease risk, whereas the shape could be “J” or “U” shaped.^{44,57,68} Third, our results assume that the samples used to define the genetic instrument for telomere length¹⁸ and the various samples used to estimate the SNP-disease associations are representative of the same general population, practically defined as being of similar ethnicity, age and sex distribution.⁷³ This assumption would, for example, not apply in the case of the SNP-disease associations derived from East Asian or pediatric populations. Generally speaking, violation of the aforementioned assumptions could bias the magnitude of the association between genetically increased telomere length and disease; but would be unlikely to increase the likelihood of false positives (i.e. incorrectly inferring an association when none exists).⁷⁴ Our results should therefore remain informative for the direction and broad magnitude of the average association at the population level, even

in the presence of such violations. Fourth, we cannot rule out chance in explaining some of the weaker findings. Fifth, our results may not be fully representative of non-communicable diseases (since not all studies shared data and our analyses were underpowered for the secondary disease outcomes). The diseases represented in our primary analyses probably account for >60% of all causes of death in American adults.⁷⁵

Clinical relevance of findings

Our findings suggest that potential clinical applications of telomere length, e.g. as a tool for risk prediction or as an intervention target for disease prevention, may have to consider a trade-off in risk between cancer and non-neoplastic diseases. For example, a number of companies have been established that offer telomere length measurement services to the public (via a requesting physician), under the claim that shorter telomeres are a general indicator of poorer health status and older biological age and that such information can be used to motivate healthy lifestyle choices in individuals. However, the conflicting direction of association between telomere length and risk of cancer and non-neoplastic diseases, indicated by our findings, suggests that such services to the general public may be premature.

Conclusion

It is likely that longer telomeres increase risk for several cancers but reduce risk for some non-neoplastic diseases, including cardiovascular diseases. Further research is required to resolve whether telomere length is a useful predictor of risk that can help guide therapeutic interventions, to clarify the shape of any dose-response relationships and to characterise the nature of the association in population subgroups.

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 383 Reis¹¹⁴; Steffen Uebe¹¹⁴; Ulrike Hüffmeier¹¹⁴; Yoshiya Kawamura¹¹⁵, Takeshi Otowa^{116, 117}
 384 and Tsukasa Sasaki¹¹⁸ on behalf of the Japanese Collaboration Team for GWAS of Panic
 385 Disorder; Martin Lloyd Hibberd¹¹⁹; Michael Levin¹²⁰; Sonia Davila¹²¹; Gang Xie^{122,20};
 386 Katherine Siminovitch^{122,20}; Jin-Xin Bei¹²³; Yi-Xin Zeng^{123,124}; Asta Försti^{125,126}; Bowang
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 388 Carlos Flores^{130,131}; Imre Noth¹³²; Shwu-Fan Ma¹³²; Jia Nee Foo¹³³; Jianjun Liu¹³³; Jong-Won
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 391 Chang¹⁴¹; Nicholas G Martin¹⁵; Scott Gordon¹⁵; Tracey Wade¹⁴²; Chaeyoung Lee¹⁴³;
 392 Michiaki Kubo¹⁴⁴; Pei-Chieng Cha¹⁴⁵; Yusuke Nakamura¹⁴⁶; Daniel Levy¹⁴⁷; Masayuki
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 394 Manichaikul¹⁵⁰; R Graham Barr¹⁵¹; Bratati Kahali¹⁵², Elizabeth Speliotes¹⁵² and Laura M
 395 Yerges-Armstrong¹⁵³ on behalf of the GOLD Consortium; Ching-Yu Cheng^{154,155,156}, Jost B.
 396 Jonas^{157,158} and Tien Yin Wong^{154,155,156} on behalf of the SEED consortium; Isabella Fogh¹⁵⁹;
 397 Kuang Lin¹⁵⁹ and John F. Powell¹⁵⁹ on behalf of the SLAGEN and ALSGEN consortia;
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400

401 Affiliations of the Telomeres Mendelian Randomization Collaboration

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403 **Acknowledgements**

404 This work was supported by CRUK grant number C18281/A19169 (the Integrative Cancer

405 Epidemiology Programme). Dr Haycock is supported by CRUK Population Research

406 Postdoctoral Fellowship C52724/A20138. The MRC Integrative Epidemiology Unit is

407 supported by grants MC_UU_12013/1 and MC_UU_12013/2. Dr Martin is supported by the

408 National Institute for Health Research (NIHR), the Bristol Nutritional Biomedical Research
409 Unit and the University of Bristol.

410

411 We gratefully acknowledge all the studies and databases that made GWAS summary data
412 available (see supplementary materials for detailed acknowledgements): **AC** (the aneurysm
413 consortium), **ALSGEN** (the International Consortium on Amyotrophic Lateral Sclerosis
414 Genetics), **AMD Gene** (Age-related Macular Degeneration Gene Consortium), **BCAC**
415 (Breast Cancer Association Consortium), **C4D** (Coronary Artery Disease Genetics
416 Consortium), **CARDIoGRAM** (Coronary ARtery DIsease Genome wide Replication and
417 Meta-analysis), **CHARGE-HF** (Cohorts for Heart and Aging Research in Genomic
418 Epidemiology Consortium – Heart Failure Working Group), **COPDGene** (The Genetic
419 Epidemiology of Chronic Obstructive Pulmonary Disease), **CORECT** (ColoRectal
420 Transdisciplinary Study), **CKDGen** (Chronic Kidney Disease Genetics consortium), **dbGAP**
421 (database of Genotypes and Phenotypes), **DIAGRAM** (DIAbetes Genetics Replication And
422 Meta-analysis), **EAGLE** (EARly Genetics & Lifecourse Epidemiology Eczema Consortium,
423 excluding 23andMe), **ECAC** (Endometrial Cancer Association Consortium), **EGG** (Early
424 Growth Genetics Consortium), **EPG** (European Periodontitis Genetics Group), **GABRIEL**
425 (A Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in
426 the European Community), **GCAN** (Genetic Consortium for Anorexia Nervosa), **GECCO**
427 (Genetics and Epidemiology of Colorectal Cancer Consortium), **GIANT** (Genetic
428 Investigation of ANthropometric Traits), **GLGC** (Global Lipids Genetics Consortium),
429 **GUGC** (Global Urate and Gout consortium), **ICBP** (International Consortium for Blood
430 Pressure), **IGAP** (International Genomics of Alzheimer's Project), **HPFS** (Health
431 Professionals Follow-Up Study), **JCTGPD** (Japanese Collaboration Team for GWAS of
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 Genetics Consortium); **KIDRISK** (Kidney cancer consortium), **MAGIC** (Meta-Analyses of
 Glucose and Insulin-related traits Consortium), **MC** (the melanoma meta-analysis
 consortium), **MESA** (Multi-Ethnic Study of Atherosclerosis), **METASTROKE/ISGC**
 (METASTROKE project of the International Stroke Genetics Consortium), **NBCS** (Nijmegen
 Bladder Cancer Study), **NHGRI-EBI GWAS catalog** (National Human Genome Research
 Institute and European Bioinformatics Institute Catalog of published genome-wide
 association studies), **NHS** (Nurses' Health Study), **OCAC** (Ovarian Cancer Association
 Consortium), **PanScan** (Pancreatic Cancer Cohort Consortium), **PGC** (Psychiatric Genomics
 Consortium), **PRACTICAL** (Prostate Cancer Association Group to Investigate Cancer
 Associated Alterations in the Genome), **SEEDS** (the Singapore Epidemiology of Eye
 Diseases Study), **SLAGEN** (Italian Consortium for the Genetics of Amyotrophic Lateral
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 Genetics Consortium), **T1Dbase** (type 1 diabetes database), **TICG** (Tourette International
 Collaborative-Genetics); **TSAICG** (Tourette Syndrome Association International Consortium
 for Genetics).

We gratefully acknowledge the assistance and contributions of Dr Julia Gummy, Ms Lisa
 Wright, Dr Georg B. Ehret (ICBP), Dr Louise V. Wain (ICBP), Dr Caroline Fox (CKDGen),
 Dr Stephan Ripke (IIBDGC), Dr Jimmy Liu (IIBDGC), Dr Carl Anderson (IIBDGC) and Dr
 Jeremiah Scharf (TSAICG and TICG).

Table 1. Single nucleotide polymorphisms associated with telomere length

SNPs	Chr	Pos	Gene	EA	OA	EAF*	Beta*	SE*	P-value*	Phet*	No. studies*	Sample size*	Discovery p-value	% variance explained	Discovery study
rs11125529	2	54248729	<i>ACYP2</i>	A	C	0.16	0.065	0.012	0.000606	0.313	6	9177	8.00E-10	0.080	Codd ²¹
rs6772228	3	58390292	<i>PXK</i>	T	A	0.87	0.041	0.014	0.049721	0.77	6	8630	3.91E-10	0.200	Pooley ¹⁷
rs12696304	3	169763483	<i>TERC</i>	C	G	0.74	0.090	0.011	5.41E-08	0.651	6	9012	4.00E-14	0.319	Codd ²²
rs10936599	3	169774313	<i>TERC</i>	C	T	0.76	0.100	0.011	1.76E-09	0.087	6	9190	3.00E-31	0.319	Codd ²¹
rs1317082	3	169779797	<i>TERC</i>	A	G	0.71	0.097	0.011	4.57E-09	0.029	6	9176	1.00E-08	0.319	Mangino ¹⁸
rs10936601	3	169810661	<i>TERC</i>	C	T	0.74	0.087	0.011	8.64E-08	0.433	6	9150	4.00E-15	0.319	Pooley ¹⁷
rs7675998	4	163086668	<i>NAF1</i>	G	A	0.80	0.048	0.012	0.008912	0.077	6	9161	4.35E-16	0.190	Codd ²¹
rs2736100	5	1286401	<i>TERT</i>	C	A	0.52	0.085	0.013	2.14E-05	0.54	4	5756	4.38E-19	0.310	Codd ²¹
rs9419958	10	103916188	<i>OBFC1</i>	T	C	0.13	0.129	0.013	5.26E-11	0.028	6	9190	9.00E-11	0.171	Mangino ¹⁸
rs9420907	10	103916707	<i>OBFC1</i>	C	A	0.14	0.142	0.014	1.14E-11	0.181	6	9190	7.00E-11	0.171	Codd ²¹
rs4387287	10	103918139	<i>OBFC1</i>	A	C	0.14	0.120	0.013	1.40E-09	0.044	6	8541	2.00E-11	0.171	Levy ²⁵
rs3027234	17	8232774	<i>CTC1</i>	C	T	0.83	0.103	0.012	2.75E-08	0.266	6	9108	2.00E-08	0.292	Mangino ¹⁸
rs8105767	19	22032639	<i>ZNF208</i>	G	A	0.25	0.064	0.011	0.000169	0.412	6	9096	1.11E-09	0.090	Codd ²¹
rs412658	19	22176638	<i>ZNF676</i>	T	C	0.35	0.086	0.010	1.83E-08	0.568	6	9156	1.00E-08	0.484	Mangino ¹⁸
rs6028466	20	39500359	<i>DHX35</i>	A	G	0.17	0.058	0.013	0.003972	0.533	6	9190	2.57E-08†	0.041	Mangino ¹⁸ & Gu
rs755017	20	63790269	<i>ZBTB46</i>	G	A	0.17	0.019	0.0129	0.339611	0.757	5	8026	6.71E-09	0.090	Codd ²¹

*Summary data from Mangino et al¹⁸; Chr, chromosome; pos, base-pair position (GRCh38.p3); EA, effect allele, OA, other allele, Beta, standard deviation change in telomere length per copy of the effect allele; SE, standard error; EAF - effect allele frequency; Phet - p value for between-study heterogeneity in association between SNP and telomere length; †from a meta-analysis of Mangino¹⁸ and Gu²⁰ performed in the present study.

Table 2. Study characteristics for primary non-communicable diseases

	No. cases	No. controls	No. SNPs	Statistical power	Pop.	Study / First author
Cancer						
Bladder cancer	1601	1819	10	0.62	EUR	NBCS ⁷⁶
Breast cancer	48155	43612	13	1.00	EUR	BCAC ^{17,77}
<i>Estrogen receptor –ve</i>	7465	42175	13	1.00	EUR	BCAC ^{17,77}
<i>Estrogen receptor +ve</i>	27074	41749	13	1.00	EUR	BCAC ^{17,77}
Colorectal cancer	14537	16922	9	1.00	EUR	CORECT/GECCO ^{64,78}
Endometrial cancer	6608	37925	12	1.00	EUR	ECAC ^{79,80}
Esophageal SCC	1942	2111	11	0.64	EA	Abnet ⁸¹
Glioma	1130	6300	12	0.72	EUR	Wrensch ⁸² & Walsh ⁶⁶
Head & neck cancer	2082	3477	12	1.00	EUR	McKay et al ⁸³
Kidney cancer	2461	5081	12	0.99	EUR	KIDRISK ⁸⁴
Lung cancer	11348	15861	13	1.00	EUR	ILCCO ⁸⁵
<i>Adenocarcinoma</i>	3442	14894	13	1.00	EUR	ILCCO ⁸⁵
<i>Squamous cell carcinoma</i>	3275	15038	13	1.00	EUR	ILCCO ⁸⁵
Skin cancer						
<i>Melanoma</i>	12814	23203	13	1.00	EUR	MC ⁸⁶
<i>Basal cell carcinoma</i>	3361	11518	13	1.00	EUR	NHS/HPFS ⁸⁷
Neuroblastoma	2101	4202	12	0.87	EUR	Diskin ⁸⁸
Ovarian cancer	15397	30816	13	1.00	EUR	OCAC ^{17,89}
<i>Clear cell</i>	1016	30816	13	0.76	EUR	OCAC ^{17,89}
<i>Endometrioid</i>	2154	30816	13	0.98	EUR	OCAC ^{17,89}
<i>Mucinous</i>	1643	30816	13	0.94	EUR	OCAC ^{17,89}
<i>Serous invasive</i>	9608	30816	13	1.00	EUR	OCAC ^{17,89}
<i>Serous LMP</i>	972	30816	13	0.73	EUR	OCAC ^{17,89}
Pancreatic cancer	5105	8739	12	1.00	EUR	PanScan (incl. EPIC) ⁹⁰
Prostate cancer	22297	22323	11	1.00	EUR	PRACTICAL ^{91,92}
Testicular germ cell cancer	986	4946	11	0.52	EUR	Turnbull ⁹³ & Rapley ⁹⁴
Autoimmune/inflammatory diseases						
Alopecia areata	2332	5233	7	0.60	EUR	Betz ⁹⁵
Atopic dermatitis	10788	30047	13	1.00	EUR	EAGLE ⁹⁶
Celiac disease	4533	10750	3	0.82	EUR	Dubois ⁹⁷
Inflammatory bowel disease						
<i>Crohn's disease</i>	5956	14927	11	1.00	EUR	IIBDGC ⁹⁸
<i>Ulcerative colitis</i>	6968	20464	12	1.00	EUR	IIBDGC ⁹⁸
Juvenile idiopathic arthritis	1866	14786	11	0.87	EUR	Thompson ^{99†}
Multiple sclerosis	14498	24091	3	1.00	EUR	IMSGC ¹⁰⁰
Aggressive periodontitis	888	6789	13	0.63	EUR	Schaefer ¹⁰¹
Rheumatoid arthritis	5538	20163	11	1.00	EUR	Stahl ¹⁰²
Cardiovascular diseases						
Abdominal aortic aneurysm	4972	99858	13	1.00	EUR	AC ^{103–108}
Coronary heart disease	22233	64762	13	1.00	EUR	CARDIoGRAM ¹⁰⁹
Heart failure	2526	20926	13	0.99	EUR	CHARGE-HF ¹¹⁰
Hemorrhagic stroke	2963	5503	12	0.96	EUR	METASTROKE/ISGC ¹¹¹
Ischemic stroke	12389	62004	13	1.00	EUR	METASTROKE/ISGC ^{112,113}
<i>large vessel disease</i>	2167	62004	13	0.99	EUR	METASTROKE/ISGC ^{112,113}
<i>small vessel disease</i>	1894	62004	13	0.97	EUR	METASTROKE/ISGC ¹¹²
<i>cardioembolic</i>	2365	62004	13	0.99	EUR	METASTROKE/ISGC ¹¹²
Sudden cardiac arrest	3954	21200	13	1.00	EUR	Unpublished
Diabetes						
Type 1 diabetes	7514	9045	6	0.95	EUR	T1DBase ^{114,115}
Type 2 diabetes	10415	53655	11	1.00	EUR	DIAGRAM ¹¹⁶
Eye disease						

AMD	7473	51177	13	1.00	EUR	AMD Gene ¹¹⁷
Retinopathy	1122	18289	12	0.75	EUR	Jensen ¹¹⁸
Lung diseases						
Asthma	13034	20638	4	1.00	EUR	Ferreira/GABRIEL ^{119,120}
COPD	2812	2534	12	0.85	EUR	COPDGene ¹²¹
Interstitial lung disease	1616	4683	9	0.60	EUR	Fingerlin ¹²²
Neurological / psychiatric diseases						
ALS	6100	7125	12	1.00	EUR	SLAGEN/ALSGEN ¹²³
Alzheimer's disease	17008	37154	12	1.00	EUR	IGAP ¹²⁴
Anorexia nervosa	2907	14860	9	0.93	EUR	GCAN ¹²⁵
Autism	4949	5314	7	0.82	EUR	PGC ¹²⁶
Bipolar disorder	7481	9250	9	1.00	EUR	PGC ¹²⁷
Major depressive disorder	9240	9519	8	0.99	EUR	PGC ¹²⁸
Schizophrenia	35476	46839	12	1.00	EUR	PGC ¹²⁹
Tourette syndrome	1177	4955	13	0.74	EUR	TICG/TSAICG ¹³⁰
Other						
Chronic kidney disease	5807	56430	13	1.00	EUR	CKDGen ¹³¹
Endometriosis	4604	9393	11	1.00	Mix	Nyholt ¹³²

Study acronyms: AC, the aneurysm consortium; **ALSGEN**, the International Consortium on Amyotrophic Lateral Sclerosis Genetics; **AMD Gene**, Age-related Macular Degeneration Gene Consortium; **BCAC**, Breast Cancer Association Consortium; **CARDIoGRAM**, Coronary ARtery Disease Genome wide Replication and Meta-analysis; **CHARGE-HF**, Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium – Heart Failure Working Group; **COPDGene**, The Genetic Epidemiology of Chronic Obstructive Pulmonary Disease; **CKDGen**, Chronic Kidney Disease Genetics consortium; **CORECT**, ColoRectal Transdisciplinary Study; **DIAGRAM**, DIAbetes Genetics Replication And Meta-analysis; **EAGLE**, EARly Genetics & Lifecourse Epidemiology Eczema Consortium (excluding 23andMe); **ECAC**, Endometrial Cancer Association Consortium; **EPIC**, European Prospective Investigation into Cancer and Nutrition study; **GABRIEL**, Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community; **GCAN**, Genetic Consortium for Anorexia Nervosa; **GECCO**, Genetics and Epidemiology of Colorectal Cancer Consortium; **IGAP**, International Genomics of Alzheimer's Project; **HPFS**, Health Professionals Follow-Up Study; **ILCCO**, International Lung Cancer Consortium; **IMSGC**, International Multiple Sclerosis Genetic Consortium; **IIBDGC**, International Inflammatory Bowel Disease Genetics Consortium; **KIDRISK**, Kidney cancer consortium; **MC**, the melanoma meta-analysis consortium; **METASTROKE/ISGC**, METASTROKE project of the International Stroke Genetics Consortium; **NBCS**, Nijmegen Bladder Cancer Study; **NHS**, Nurses' Health Study; **OCAC**, Ovarian Cancer Association Consortium; **PanScan**, Pancreatic Cancer Cohort Consortium; **PGC**, Psychiatric Genomics Consortium; **PRACTICAL**, Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome; **SLAGEN**, Italian Consortium for the Genetics of Amyotrophic Lateral Sclerosis; **T1DBase**, type 1 diabetes database; **TICG** (Tourette International Collaborative-Genetics); **TSAICG** (Tourette Syndrome Association International Consortium for Genetics); **Abbreviations:** **ALS**, amyotrophic lateral sclerosis; **AMD**, age-related macular degeneration; **COPD**, chronic obstructive pulmonary disease; **EUR**, European; **EA**, East Asian; **LMP**, low malignant potential; **No.**, number; **Pop.**, population; **SCC**, squamous cell carcinoma; **SNP**, single nucleotide polymorphism; **-ve**, negative; **+ve**, positive; †plus previously unpublished data.

Figure 1. The association between genetically increased telomere length and odds of primary non-communicable diseases

Legend to Figure 1

*P value for association between genetically increased telomere length and disease from maximum likelihood; the effect estimate for heart failure is a hazard ratio (all others are odds ratios); P_{het} , P-value for heterogeneity amongst SNPs within the instrument; COPD, chronic obstructive pulmonary disease; SNP, single nucleotide polymorphism; CI, confidence interval; LMP, low malignancy potential; ER, estrogen receptor; -VE, negative; +VE, positive.

Figure 2. The association between genetically increased telomere length and odds of cancer as a function of selected characteristics

Legend to Figure 2

The plotted data show how the strength of the relationship between genetically increased telomere length and cancer varies by the selected characteristic. The R^2 statistic indicates how much of the variation between cancers can be explained by the selected characteristic. P-values are from meta-regression models. Circle sizes are proportional to the inverse of the variance of the log odds ratio. The hashed line indicates the null of no association between telomere length and cancer (i.e. an odds ratio of 1). Data for percentage survival 5 years after diagnosis, cancer incidence and median age-at-diagnosis was downloaded from the Surveillance, Epidemiology, and End Results Program.³³ Data for average lifetime number of stem cell divisions was downloaded from Tomasetti and Vogelstein.³⁴ Not all cancers had information available for the selected characteristics (hence the number of cancers varies across the subplots). Information was available for 9 cancers for tissue-specific rates of stem cell division, 13 cancers for percentage surviving 5 years post-diagnosis, 17 cancers for cancer incidence and 13 cancers for median age-at-diagnosis. SD, standard deviation; OR, Odds ratio.

Figure 3. Comparison of genetic and prospective observational studies[†] of the association between telomere length and disease

Legend to Figure 3

*from fixed-effects meta-analysis of independent observational studies described in Table S3; [†]search strategy and characteristics for observational studies are described in Tables S3 and S4; ‡CCHS and CGPS; +PLCO, ATBC & SWHS (acronyms explained in Table S3); CI, confidence interval

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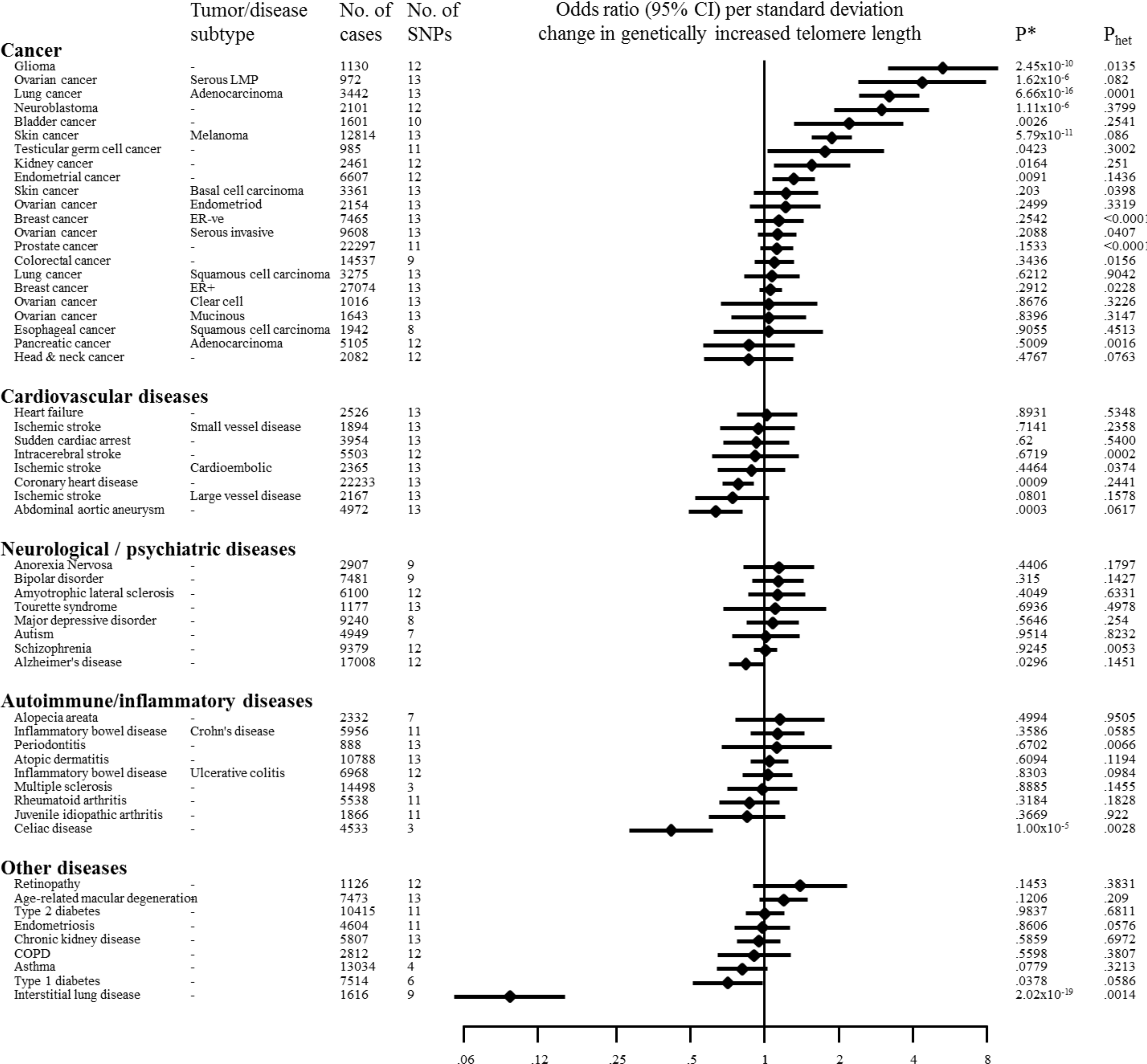
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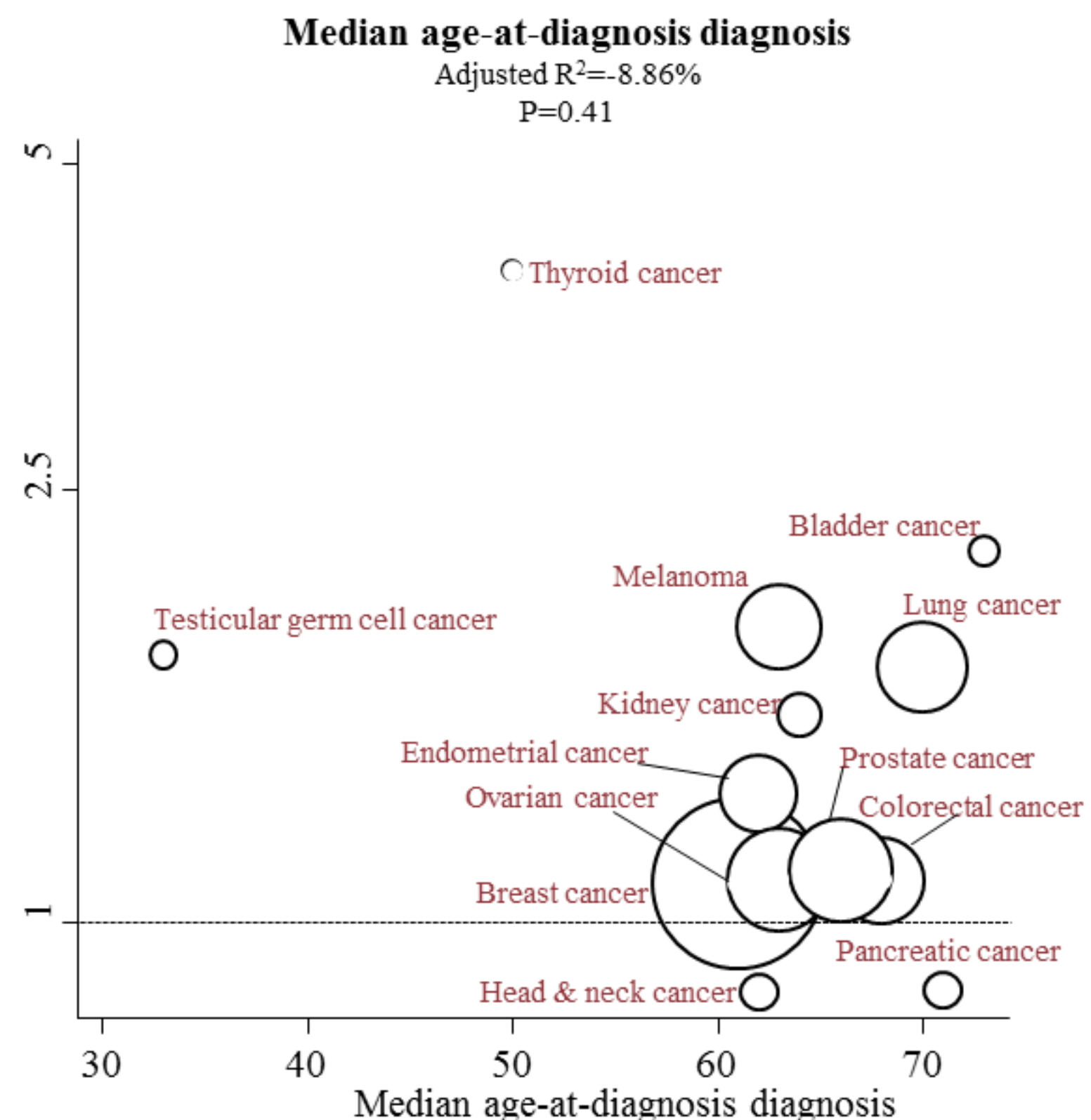
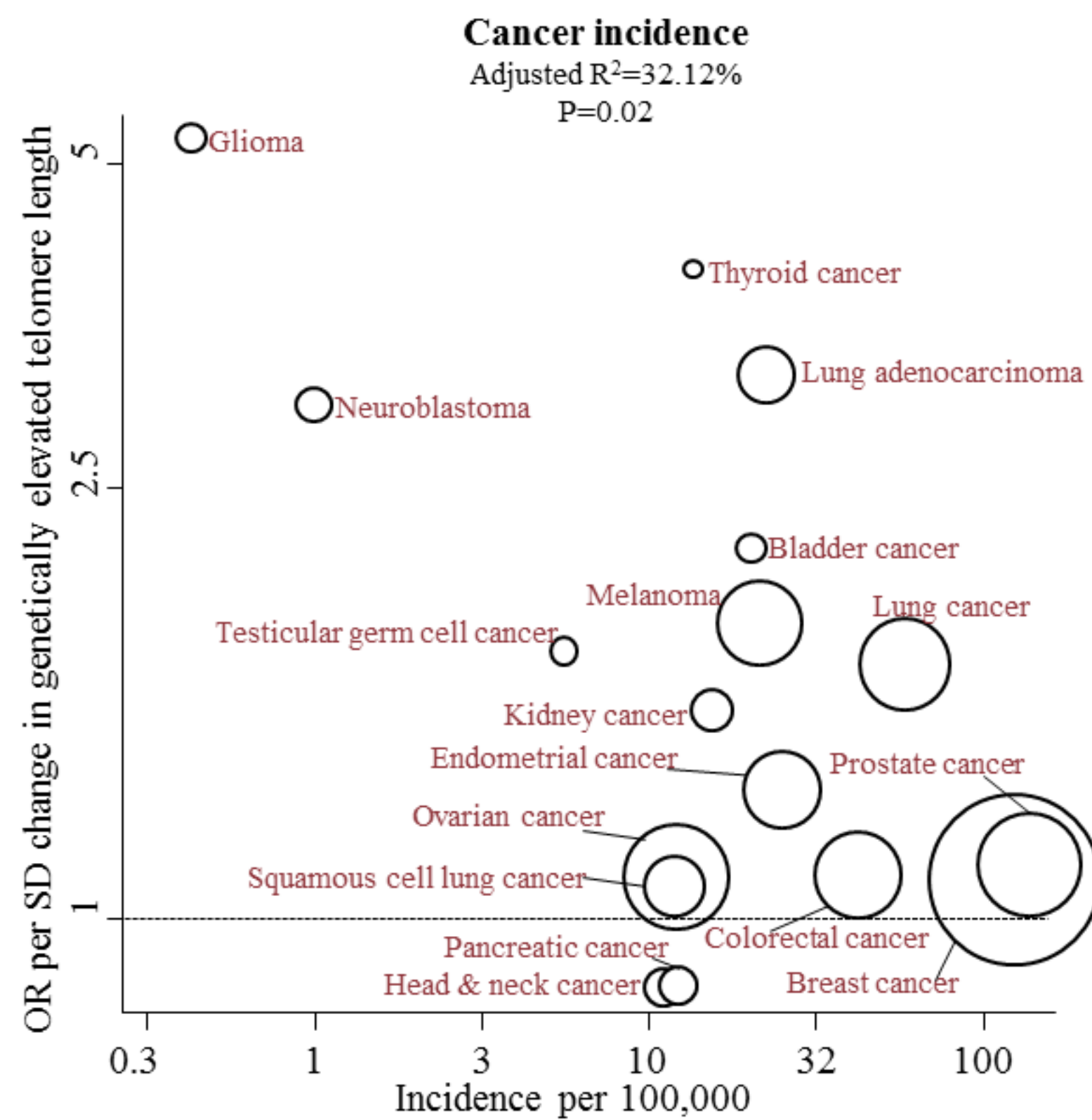
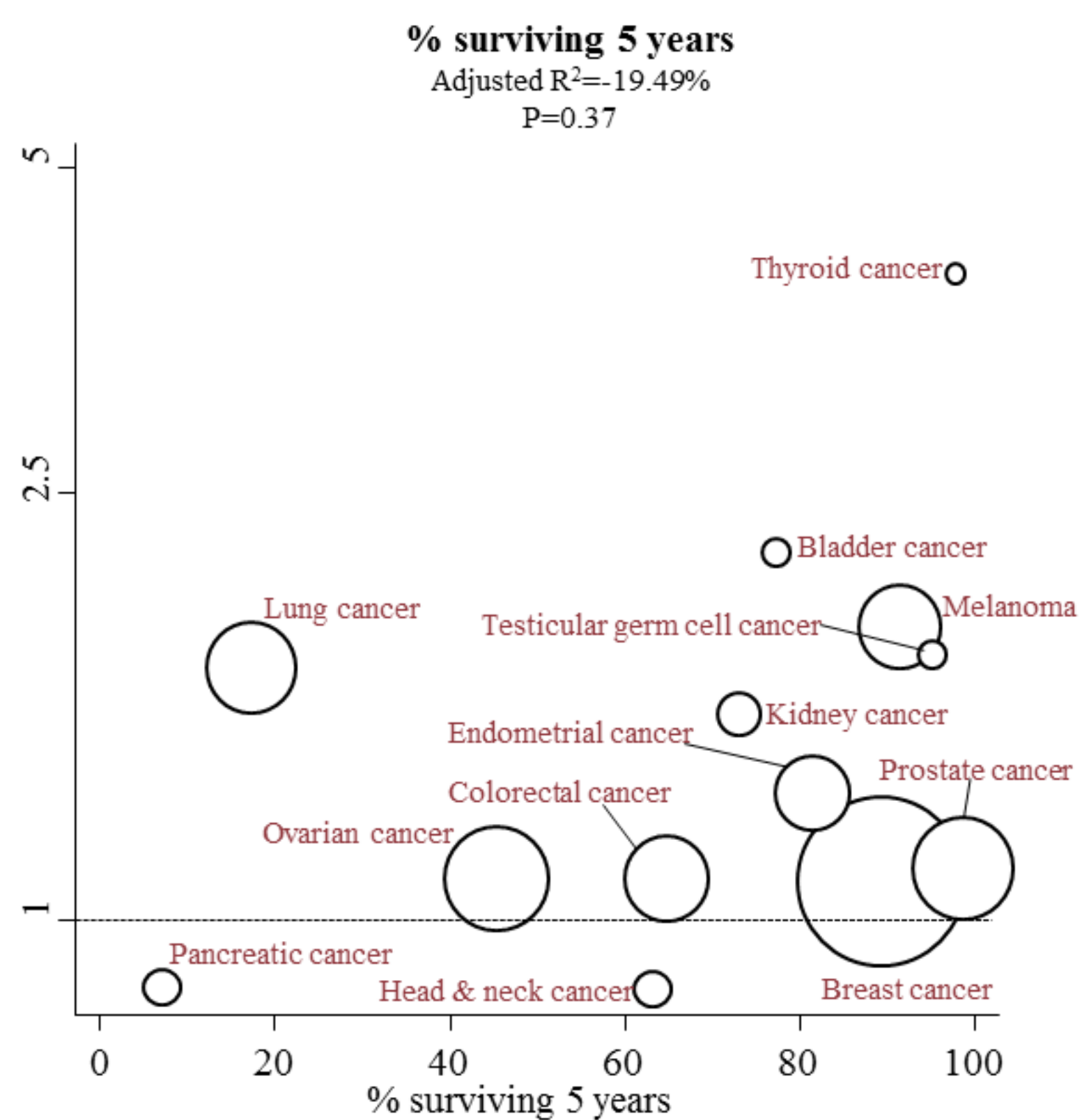
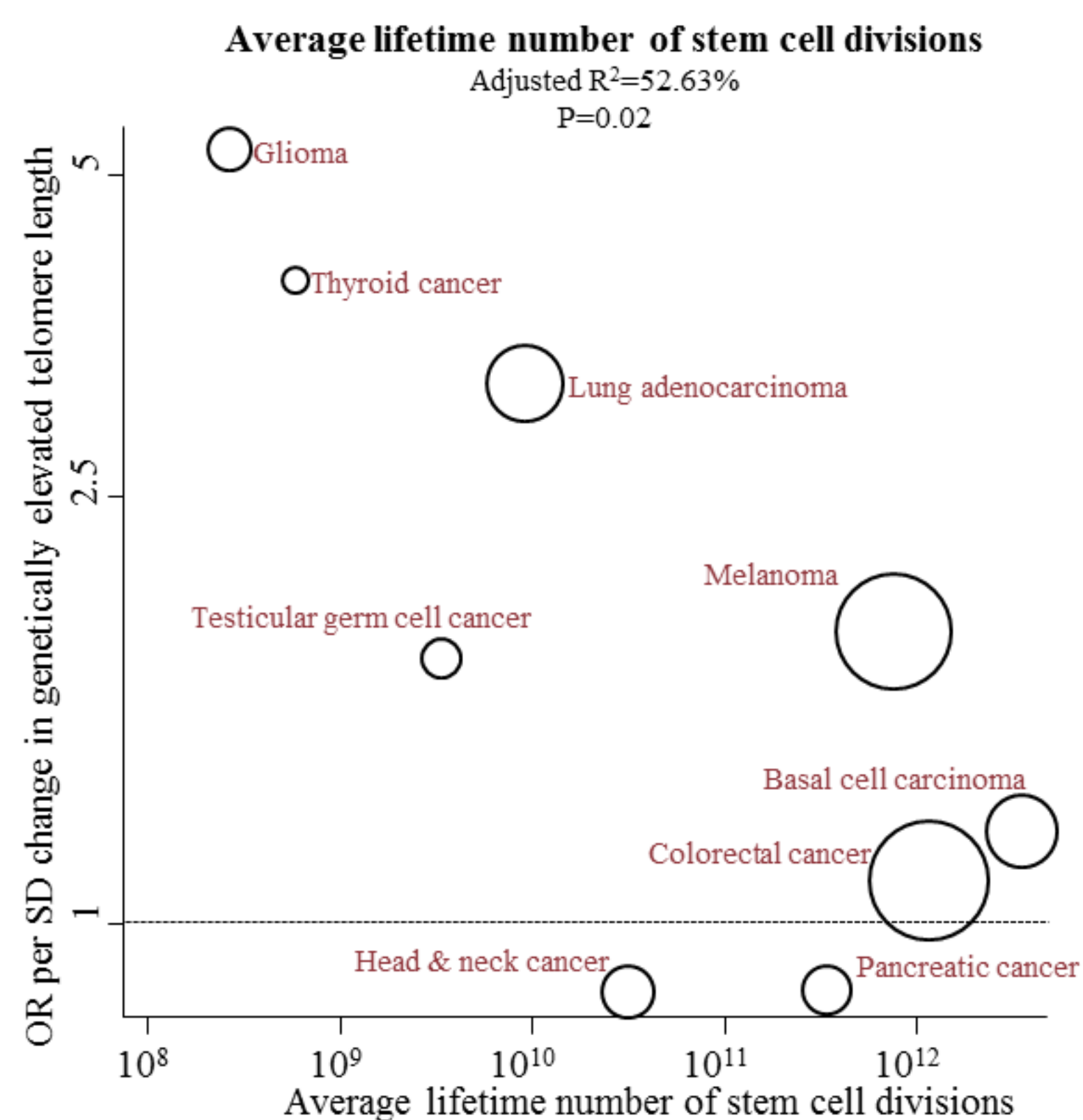
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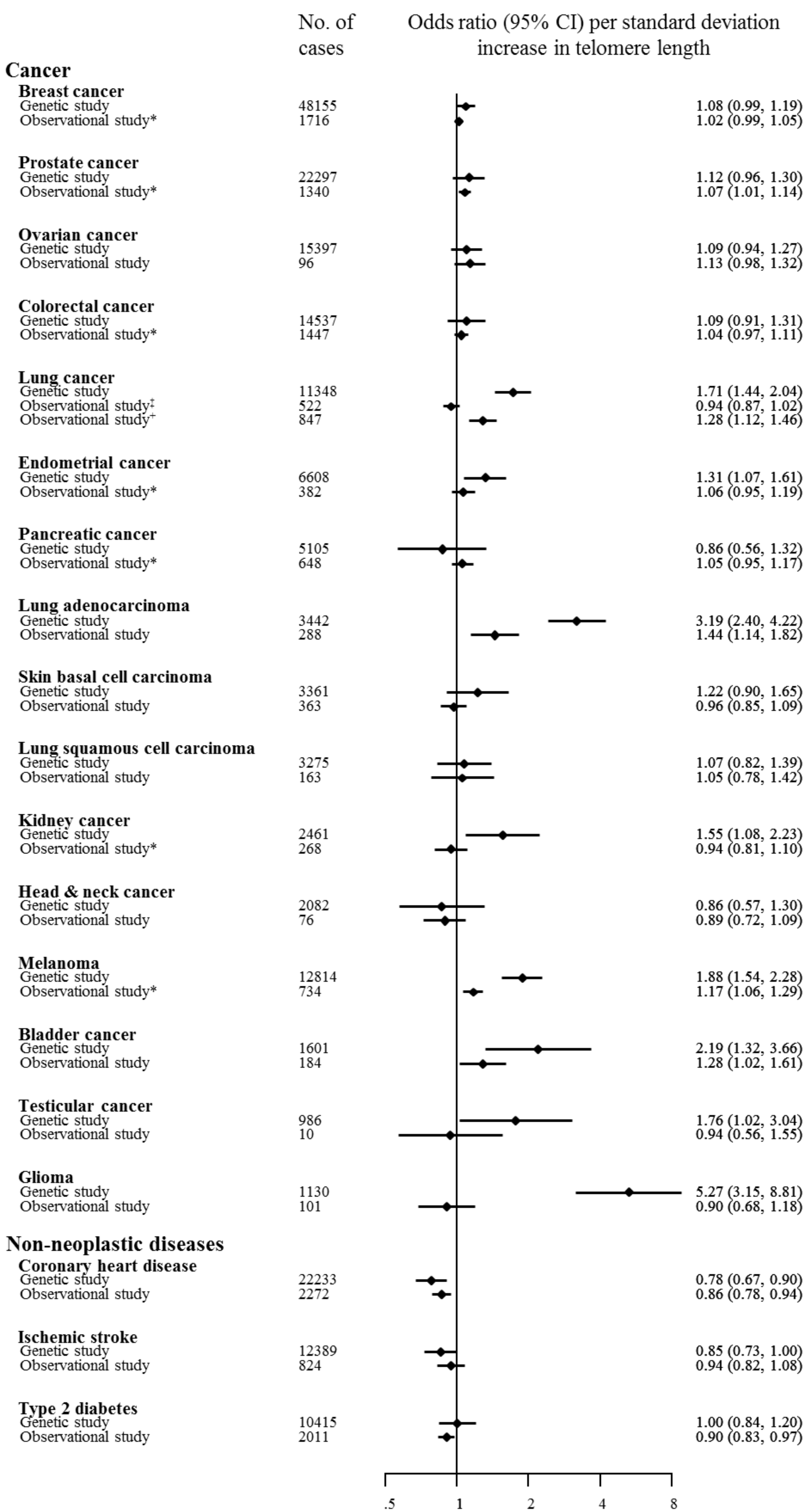
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802







1 **Supplementary material**

2 **Mendelian randomization study of the association between telomere length and risk of cancer**
3 **and non-neoplastic diseases**

4

5 The Telomeres Mendelian Randomization Collaboration

6

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96

97 SUPPLEMENTARY METHODS

98

99 Additional details on the design strategy

100

101 *Identification of genetic instruments for telomere length*

102 To identify genetic variants to serve as instruments for telomere length, we searched the genome-
103 wide association study (GWAS) catalog^{1,2} on the 15 January 2015, to identify reported single
104 nucleotide polymorphisms (SNPs) associated with telomere length. To supplement the list with
105 additional potential instruments, we also searched the original study reports curated by the GWAS
106 catalog.³⁻¹¹ We included all ‘telomere length’ SNPs in the GWAS catalog as potential proxies,
107 regardless of their reported P-value, but used a P-value threshold of $<5 \times 10^{-8}$ (the conventional
108 threshold for declaring association in GWAS) for SNPs identified from original study reports (if
109 these were not already curated by the GWAS catalog). We acquired summary data for all SNPs
110 identified by the above strategy from a meta-analysis of six GWASs of leukocyte telomere length,
111 conducted in 9,190 participants of European ancestry.⁴ Telomere length in the six studies was
112 measured by Southern blotting. GWAS analyses in the 6 studies were adjusted for age, sex, body
113 mass index and smoking history. The genomic control inflation factor (λ_{GC}) ranged from 0.995 to
114 1.076 across the six studies, indicating little evidence for confounding by population stratification.⁴
115 The following summary data were acquired for each SNP from each of the six studies: the
116 regression coefficient (beta) and its standard error, where the beta reflects the change in telomere
117 length (in base pair units) per copy of the effect allele; the effect allele; the non-effect allele; and
118 effect allele frequency. We combined the effect estimates from the six separate studies by fixed
119 effects meta-analysis. We then excluded SNPs if they lacked strong evidence of association with
120 telomere length. We defined strong evidence of association as a P value $<5 \times 10^{-8}$ in: i) the discovery
121 stage of at least one published GWAS of telomere length³⁻¹⁰ or ii) a meta-analysis of summary data

122 from Mangino et al⁴ and other GWASs of telomere length,^{3,5–10} with any overlapping studies
123 excluded from Mangino et al.⁴ We also excluded SNPs with a minor allele frequency <0.05 or
124 showing strong evidence of between-study heterogeneity in associations with telomere length
125 ($P \leq 0.001$).

126

127 *Acquisition of summary data from disease and risk factor studies*

128 We extracted the following summary data for each genetic instrument for telomere length from
129 GWASs of diseases and risk factors: the regression coefficient (beta) and its standard error, the
130 effect allele, the non-effect allele and effect allele frequency. For binary traits, the beta
131 corresponded to the log odds ratio per copy of the effect allele. For quantitative traits, the beta
132 corresponded to the unit change in the trait per copy of the effect allele. We harmonized the
133 summary data for diseases and risk factors so that the effect allele reflected the allele associated
134 with longer telomeres. When SNPs were palindromic, i.e. A/T or G/C, we used information on
135 allele frequency to resolve strand ambiguity. We also requested the following metrics of SNP
136 genotype quality: P-values for Hardy-Weinberg equilibrium (HWE), imputation quality scores and
137 P-values for between-study heterogeneity. We also estimated the percentage overlap in participants
138 amongst the telomere length and disease and risk factor GWASs. When reported, statistics on
139 between-study heterogeneity, Hardy-Weinberg equilibrium and imputation quality were used to
140 exclude low quality SNPs from disease and risk factor studies, using the following criteria: strong
141 evidence of between-study heterogeneity in the SNP-phenotype association ($P \leq 0.001$), Hardy-
142 Weinberg disequilibrium ($P \leq 0.001$) or imputation quality metric (info or r^2) ≤ 0.90 .

143

144 *Power calculations*

145 Power calculations for disease outcomes were implemented using the method described by
146 Burgess¹² and assumed an odds ratio of ≥ 2.0 per standard deviation higher telomere length and an
147 alpha of 0.01. Power calculations for risk factors for non-communicable diseases were similar,

except that a ≥ 0.5 standard deviation change in quantitative risk factors and an odds ratio of ≥ 1.5 for binary risk factors was assumed for each standard deviation change in telomere length. When more than one study was available for the same outcome trait, priority was given to the study with the higher statistical power. Power calculations took into account the variance explained in telomere length by each SNP, inferred from published reports,^{3–10} and the sample size available for each outcome.

154

155 **Estimating the association between genetically increased telomere length and outcome traits**

156 We employed three general approaches for estimating the association between genetically increased
157 telomere length and outcome traits. Our main results are based on a likelihood-approach.¹³
158 Sensitivity analyses were based on two approaches: the weighted median¹⁴ and MR-Egger
159 regression.¹⁵ The technical details of these approaches are described below.

160

161 Prior to calculating the associations of genetically increased telomere length with diseases and risk
162 factors, we estimated the pairwise r^2 for all telomere-associated SNPs residing on the same
163 chromosome using PLINK¹⁶ and 1000 Genomes phase 3 data for European samples.¹⁷ SNPs
164 residing on separate chromosomes or separated by more than 50 megabases on the same
165 chromosome were assumed to be in linkage equilibrium. The genetic instruments for telomere
166 length were pruned so that no SNP pair had an $r^2 > 0.9$ (strong linkage disequilibrium), using the
167 ‘indep’ command in PLINK.¹⁶ The base pair position and chromosome id for each SNP, in
168 GRCCh38 format, was extracted from Ensembl through the R biomart package.^{18–20} Linkage
169 disequilibrium between the remaining SNPs was taken into account using a variance-covariance
170 matrix (described below). For analyses in which SNP-disease associations were derived from East
171 Asian populations, genetic instruments were further pruned so that no SNP pair had an $r^2 > 0.1$
172 (because the variance-covariance matrix used to model the correlation between SNPs was based on
173 a European population).

174

175 *Likelihood approach*

176 We combined summary data across SNPs into a single instrument, using maximum likelihood to
 177 estimate the slope of the relationship between β_{GD} and β_{GP} and a variance-covariance matrix to make
 178 allowance for linkage disequilibrium between SNPs, where β_{GD} is the change in the outcome trait
 179 per copy of the effect allele and β_{GP} is the standard deviation change in telomere length per copy of
 180 the effect allele.¹³ The standard deviation of telomere length corresponds to approximately 650 base
 181 pairs.⁴ The variance-covariance matrix was estimated using 1000 Genomes phase 3 data for
 182 Europeans.¹³ The model that is fitted is:

$$\begin{pmatrix} \beta_{GP} \\ \beta_{GD} \end{pmatrix} \sim N_{2K} \left(\begin{pmatrix} \xi \\ \beta_{IV}\xi \end{pmatrix}, \begin{pmatrix} \Sigma_{PP} & \Sigma_{PD} \\ \Sigma_{DP} & \Sigma_{DD} \end{pmatrix} \right)$$

183 where β_{GP} is a vector of the SNP-telomere-length associations, β_{GD} is a vector of the SNP-disease
 184 associations, β_{IV} is the causal effect parameter, K is the number of SNPs, Σ_{PP} is a variance-
 185 covariance matrix with elements $(\Sigma_{PP})_{ij} = se(\beta_{GPI})se(\beta_{GPj})\rho_{ij}$ where $se(\beta_{GPI})$ is the standard
 186 error of the SNP-telomere-length association for the i th genetic variant, and ρ_{ij} is the correlation
 187 between the i th and j th variants due to linkage disequilibrium. Components of Σ_{DD} are similarly
 188 defined as $(\Sigma_{DD})_{ij} = se(\beta_{GDI})se(\beta_{GDj})\rho_{ij}$, and $\Sigma_{PD} = \Sigma_{DP} = 0$ due to the two-sample setting
 189 (sensitivity analyses in a previous study¹³ suggested results were robust to some correlation between
 190 the gene-phenotype and gene-outcome associations that may arise due to sample overlap). The
 191 slope estimated by maximum likelihood can be interpreted as the log odds ratio for disease per
 192 standard deviation change in genetically increased telomere length. The slope can further be
 193 interpreted as the causal effect of telomere length on disease if Mendelian randomization
 194 assumptions hold. The assumptions are: the SNPs are associated with telomere length (IV1); the
 195 SNPs are independent of confounders (IV2); and the SNPs are independent of disease adjusted for
 196 telomere length and confounders (IV3). See Supplementary Figure S7 for further details of the
 197 Mendelian randomization assumptions and Supplementary Table S6 for a glossary of terms.

198

199 *The weighted median approach*¹⁴

200 Let $\hat{\beta}_{(1)}, \dots, \hat{\beta}_{(J)}$ represent the J causal effect estimates ordered from smallest ($\hat{\beta}_{(1)}$) to largest ($\hat{\beta}_{(J)}$).

201 Now define

202 $w_{(j)}^* = \frac{w_j}{S_j}, \quad \text{where } S_j = \sum_j w_j,$

203 where w_j is the inverse variance of $\hat{\beta}_{(j)}$,

204 and equate $\hat{\beta}_{(j)}$ with a quantile, $p_{(j)}^w$, defined as

205
$$p_{(j)}^w = \frac{100}{S_j} \left(S_{(j)} - \frac{w_{(j)}}{2} \right).$$

206 $p_{(j)}^w$ represents the quantile from the weighted empirical distribution function of the ordered

207 estimates $\hat{\beta}_{(1)}, \dots, \hat{\beta}_{(J)}$. The weighted median estimate, $\hat{\beta}_{WM}$ is defined as the 50th percentile of this

208 weighted distribution. Typically the 50th percentile will lie between two estimates ($\hat{\beta}_{(l)}$ and $\hat{\beta}_{(m)}$,

209 say), in which case $\hat{\beta}_{WM}$ is found by linear interpolation. $\hat{\beta}_{WM}$ is a consistent estimate for β provided

210 that at least 50% of the ‘weight’ making up S_j comes from genetic variants that are valid

211 instruments. In other words, the weighted median function provides a valid estimate of the causal

212 effect of telomere length on disease if at least half of the genetic information comes from valid

213 instruments (assumptions illustrated in Supplementary Figure S7; glossary of terms in

214 Supplementary Table S6).¹⁴

215

216 *The MR-Egger approach*

217 The MR-Egger method¹⁵ performs a weighted linear regression of the SNP-disease coefficients on

218 the SNP-exposure coefficients (where exposure in this study is telomere length):

219
$$\frac{\hat{\Gamma}_j}{\sigma_{Yj}} = \frac{\beta_{0E}}{\sigma_{Yj}} + \beta_{1E} \frac{\hat{\gamma}_j}{\sigma_{Yj}}$$

where Γ corresponds to the SNP-disease coefficients, γ corresponds to the SNP-exposure coefficients and σ_{y_j} is the standard error of $\hat{\Gamma}_j$. If all SNPs are valid instruments, then $\beta_{0E} = 0$. The value of $\hat{\beta}_{0E}$ can be interpreted as an estimate of the average pleiotropic effect across the SNPs. An intercept term that differs from zero is indicative of overall directional pleiotropy. The MR-Egger estimate for β , $\hat{\beta}_{1E}$, is consistent even if *all* SNPs are invalid, provided that

- Across all SNPs, the magnitude of the SNP-exposure associations are independent of their pleiotropic effects (also known as the InSIDE [Instrument Strength Independent of Direct Effect] assumption)
- The number of SNPs, J , grows large (i.e. tends to infinity).

See Supplementary Figure S7 for further details on the assumptions and Supplementary Table S6 for a glossary of terms.

SUPPLEMENTARY RESULTS

In analyses of secondary cancer outcomes, genetically increased telomere length was associated with thyroid cancer, chronic lymphocytic leukemia and multiple myeloma ($P < 0.05$) (Supplementary Figure S2). In analyses of secondary non-neoplastic diseases, genetically increased telomere length was associated with reduced odds of panic disorder ($P < 0.05$) (Supplementary Figure S2). In secondary analyses of 44 risk factors for non-communicable diseases (Supplementary Table S2), genetically increased telomere length was associated with increased pulse pressure, systolic blood pressure, diastolic blood pressure, mean arterial pressure, triglycerides, uric acid and education and with decreased HDL cholesterol, mean corpuscular haemoglobin and mean corpuscular volume ($P < 0.05$) (Supplementary Figure S5). There was some evidence for an association between genetically increased telomere length and ever smoking status ($P = 0.03$, Supplementary Figure S6) but this association is unlikely to be reliable given that the SNP-telomere-length associations were adjusted for smoking history; the association may therefore reflect collider bias.²¹

246 SUPPLEMENTARY DISCUSSION

247 Mechanisms of association between SNPs and telomere length

248 The mechanisms of the underlying associations between the selected SNPs and telomere length are
249 generally unknown. Some of the SNPs are located in or near the *TERC* or *TERT* genes, suggesting
250 that the mechanism could involve the telomerase enzyme, as well as the *OBFC1* and *CTCI* genes,
251 which have known roles in regulation of telomere length biology (Table 1). *OBFC1* is an enzyme
252 involved in initiating DNA replication and is involved in the telomere-associated CST complex.²²
253 *CTCI* encodes a component of the CST complex, which plays a role in protecting telomeres from
254 degradation.

255

256 Bias from sample overlap and strength of the association between SNPs and telomere length

257 The selected genetic instruments for telomere length correspond to 10 independent genomic loci
258 and collectively account for 2-3% of the variance in leukocyte telomere length. The corresponding
259 F statistic is around 18, which means that bias due to weak instruments is unlikely to be substantial
260 even if there were considerable overlap amongst the telomere length and disease and risk factor
261 GWASs.²³ The estimated overlap in participants amongst the telomere length and outcome GWASs
262 was less than 11% for all diseases and risk factors, except for hepatic steatosis, for which overlap
263 was around 51%, indicating that the vast majority of our results should be robust to weak
264 instrument bias.

265

266 Misconceptions about Mendelian randomization

267 A common misconception about Mendelian randomization studies is that genetic instruments
268 should explain a substantial proportion of the variation in target exposures (e.g. telomere length in
269 this study) in order to provide robust inferences about exposure-disease associations. However, if
270 the genetic instruments are valid (i.e. conform to Mendelian randomization assumptions,

Supplementary Figure S7), the variation explained by the instrument only affects statistical power and does not generally affect validity of the causal inference. In this sense, genotype assignment in a Mendelian randomization study is analogous to treatment assignment in a randomized controlled trial, e.g. of blood pressure lowering drugs.²⁴ Although experimental interventions to reduce blood pressure may only explain a small fraction of the total variation in blood pressure in a typical RCT, we can still make causal inferences about blood pressure as a whole (and not just the proportion of variation in blood pressure due to the experimental intervention). Moreover, the aim of Mendelian randomization studies is to make inferences at the population level and not the individual level (for which genetic proxies of substantial explanatory power would be required).²⁴ If Mendelian randomization assumptions were violated, however, then the limited variation explained by our genetic instruments might not behave in similar manner to other sources of variation in telomere length, which would undermine our ability to draw causal inferences. See the above section ‘Estimating the association between genetically increased telomere length and outcome traits’ and Supplementary Figure S7 for details on the assumptions. See Supplementary Table S6 for an explanation of Mendelian randomization terminology. See Haycock et al²⁵ and Davey Smith and Hemani²⁶ for reviews on Mendelian randomization.

287

Potential for confounding by population stratification, ancestry and age

It is unlikely that confounding by population stratification, ancestry or age (an important confounder of observational studies of telomere length) can account for our results. The 15 primary diseases showing some evidence of association with telomere length (defined as a P value<0.05) were 100% European, on the basis of self reported ancestry or genetic analyses (individuals showing genetic evidence of non-European ancestry were excluded).^{3,27-44} In addition, these studies all made some allowance for population stratification in their analyses: 12 adjusted for principal component scores of genetic variation in their models or applied genomic control corrections to their results; and 3 concluded there was little evidence for population stratification, on the basis of

297 visual inspection of Quantile-Quantile plots of GWAS results (i.e. lambdas for genomic inflation
298 were close to 1). The GWAS we used to defined genetic instruments for telomere length⁴ also
299 adjusted for principal component scores; and lambdas for genomic inflation were close to 1. Since
300 our MR analyses will have inherited any adjustments made in the original analyses, it is therefore
301 unlikely that confounding by ancestry or population stratification can explain our results.

302 Confounding by age is also unlikely, given the random distribution of genotypes in the general
303 population with respect to lifestyle and other environmental factors, as well as the fixed nature of
304 germline genotypes. Consistent with this expectation, we did not observe an association between
305 subject age and their genetically predicted telomere length values in our previous studies.^{44,45}

306

307 **Associations with non-neoplastic diseases**

308 The inverse associations observed for coronary heart disease, abdominal aortic aneurysm, celiac
309 disease and interstitial lung disease are compatible with findings based on observational and
310 Mendelian randomization studies of telomere length as well as dyskeratosis congenita (a congenital
311 disease characterized by chronically short telomeres).⁴⁶⁻⁵⁰

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Supplementary Table S1. Study characteristics for secondary non-communicable diseases and diseases from independent studies for replication analyses

	No. cases	No. controls	No. SNPs	Statistical power	Pop.	First author /database
Cancer						
Chronic lymphocytic leukemia	2883	8350	1	0.22	EUR	Speedy/GWAS cat. ⁵¹
Chronic myeloid leukemia	201	497	8	0.07	EA	Kim ⁵²
Ewing's sarcoma	401	684	4	0.06	EUR	Postel-Vinay ⁵³
Follicular lymphoma	212	748	3	0.04	EUR	Conde ⁵⁴
Gallbladder cancer	41	866	2	0.01	EA	Cha ⁵⁵
Gastric cancer						
<i>Cardia adenocarcinoma</i>	1126	2111	11	0.47	EA	Abnet ⁵⁶
<i>Noncardia adenocarcinoma</i>	632	2111	11	0.29	EA	Abnet ⁵⁶
Multiple myeloma	4692	10990	1	0.37	EUR	Chubb/GWAS cat. ⁵⁷
Nasopharyngeal carcinoma	1583	1894	2	0.17	EA	Bei ⁵⁸
B-cell Non-Hodgkin lymphoma	253	1438	10	0.13	EA	Tan ⁵⁹
Skin squamous cell carcinoma	449	11518	13	0.34	EUR	Zhang ⁶⁰
Thyroid cancer	649	431	12	0.16	EUR	Kohler ⁶¹
Upper gastrointestinal cancers	3523	2100	2	0.28	EA	Li/dbGAP ⁶²
Autoimmune/inflammatory diseases						
Inflammatory psoriatic arthritis	609	990	13	0.29	EUR	Huffmeier ⁶³
Kawasaki disease	405	6252	11	0.26	EUR	Khor ⁶⁴
Narcolepsy	1188	1985	9	0.46	EA	Han ⁶⁵
Psoriasis	1139	1132	9	0.34	EA	Zhang ⁶⁶
Sarcoidosis	564	1575	9	0.16	EUR	Fischer ⁶⁷
Systemic lupus erythematosus	1311	1783	4	0.20	EUR	Hom/dbGAP ⁶⁸
Vitiligo	1117	1429	2	0.12	EA	Quan ⁶⁹
Wegener's granulomatosis	459	1503	10	0.20	EUR	Xie ⁷⁰
Neurological / psychiatric diseases						
Bulimia nervosa	151	2291	8	0.07	EUR	Wade ⁷¹
Panic disorder	718	1717	8	0.28	EA	JCTGPD ⁷²
Parkinson's disease	1713	3978	4	0.35	EUR	Simón-Sánchez/dbGAP ⁷³

Other

Hirschsprung's disease	173	615	6	0.04	EA	Tang ⁷⁴
Paget's disease	741	2699	12	0.43	EUR	Albagha ⁷⁵
Vascular dementia	84	200	8	0.03	EA	Kim ⁷⁶

Independent disease studies for replication analyses

Bladder cancer	7712	13125	1	0.56	EUR	Figueroa/GWAS cat. ⁷⁷
Colorectal cancer	728	3282	9	0.39	EA	Zhang ⁷⁸
Coronary heart disease	15399	15050	4	1.00	Mix	C4D ⁷⁹
Glioma	1854	4955	1	0.12	EUR	GliomaScan/GWAS cat. ⁸⁰
Interstitial lung disease†	542	542	11	0.15	EUR	Noth ⁸¹
Interstitial lung disease‡	242	1469	1	0.02	EA	Mushiroda/GWAS cat. ⁸²
Pancreatic cancer	4164	3792	10	0.90	EUR	PanC4 ⁸³
Multiple sclerosis	978	883	4	0.11	EUR	Baranzini/dbGAP ⁸⁴
Nasopharyngeal carcinoma	277	285	2	0.03	EA	Tse ⁸⁵
Type 2 diabetes	8569	8923	10	1.00	EA	Li ⁸⁶

†≤17% cases overlapped with cases from Fingerlin et al³¹ and 77% of cases had idiopathic pulmonary fibrosis; ‡all cases had idiopathic pulmonary fibrosis.

Study/database acronyms: C4D, Coronary Artery Disease Genetics Consortium; dbGAP, summary data downloaded from the database of Genotypes and Phenotypes; GWAS cat., data downloaded from the National Human Genome Research Institute/European Bioinformatics Institute Catalog of published genome wide association studies; JCTGPD, Japanese Collaboration Team for GWAS of Panic Disorder. **Abbreviations:** EUR, European; EA, East Asian; No., number; Pop., population; SNP, single nucleotide polymorphism.

Supplementary Table S2. Study characteristics of 44 risk factors for non-communicable diseases

	Sample size	SD	Units	No. of SNPs	Stat. power	Pop.	First author / study
Anthropometric							
Birth length	22557	2.0	cm	12	1.00	EUR	EGG ⁸⁷
Birth weight	26836	547.5	g	12	1.00	EUR	EGG ⁸⁸
Body mass index	241253	4.8	kg/m ²	13	1.00	EUR	GIANT ⁸⁹
Childhood obesity	13848	NA	log _e odds	12	0.78	EUR	EGG ⁹⁰
Head circumference	10705	1.5	cm	13	1.00	EUR	EGG ⁹¹
Height	253288	0.1	m	13	1.00	EUR	GIANT ⁹²
Hip circumference	224459	8.5	cm	13	1.00	EUR	GIANT ⁹³
Waist circumference	224459	12.5	cm	13	1.00	EUR	GIANT ⁹³
Waist-to-hip ratio	224459	0.1	ratio	13	1.00	EUR	GIANT ⁹³
Smoking behaviors							
Age of smoking initiation	47961	0.3	log _e years	13	1.00	EUR	TAG ⁹⁴
Cigarettes smoked per day	68028	11.7	CPD	13	1.00	EUR	TAG ⁹⁴
Ever smoker	74035	NA	log _e odds	13	1.00	EUR	TAG ⁹⁴
Ex smoker	41969	NA	log _e odds	13	1.00	EUR	TAG ⁹⁴
Blood pressure							
Diastolic blood pressure	66466	10.7	mm Hg	12	1.00	EUR	ICBP ⁹⁵
Mean arterial pressure	27803	12.8	mm Hg	13	1.00	EUR	ICBP ⁹⁶
Pulse pressure	70903	13.5	mm Hg	13	1.00	EUR	ICBP ⁹⁶
Systolic blood pressure	66473	18.2	mm Hg	12	1.00	EUR	ICBP ⁹⁵
Education							
College completion	95427	NA	log _e odds	13	1.00	EUR	SSGAC ⁹⁷
Years of educational attainment	126559	1.2	years	13	1.00	EUR	SSGAC ⁹⁷
Glycemic							
2 hr glucose	15234	1.27	mmol/L	11	1.00	EUR	MAGIC ⁹⁸
Beta-cell function (HOMA-B)	46186	0.96	log _e HOMA	12	1.00	EUR	MAGIC ⁹⁹
Fasting glucose	46186	0.73	mmol/L	12	1.00	EUR	MAGIC ⁹⁹
Fasting insulin	38238	0.79	log _e pmol/L	12	1.00	EUR	MAGIC ⁹⁹

Fasting proinsulin	10701	0.81	log _e pmol/L	12	1.00	EUR	MAGIC ⁹⁹
Glycated hemoglobin (HbA1c)	46368	0.53	%	12	1.00	EUR	MAGIC ¹⁰⁰
Insulin resistance (HOMA-IR)	46186	0.67	log _e HOMA	12	1.00	EUR	MAGIC ⁹⁹
Hematological							
Hemoglobin	54287	1.3	g/dL	12	1.00	EUR	van der Harst ¹⁰¹
Mean cell hemoglobin	45969	1.99	pg	12	1.00	EUR	van der Harst ¹⁰¹
Mean cell hemoglobin concentration	49632	1.01	g/dL	12	1.00	EUR	van der Harst ¹⁰¹
Mean cell volume	51277	5.2	fL	12	1.00	EUR	van der Harst ¹⁰¹
Packed cell volume	46848	5.9	%	12	1.00	EUR	van der Harst ¹⁰¹
Red blood cell count	47873	0.5	10 ¹² /L	12	1.00	EUR	van der Harst ¹⁰¹
Lipids							
HDL cholesterol	103019	15.51	mg/dL	11	1.00	EUR	GLGC ¹⁰²
LDL cholesterol	97562	38.67	mg/dL	11	1.00	EUR	GLGC ¹⁰²
Total cholesterol	103266	41.75	mg/dL	11	1.00	EUR	GLGC ¹⁰²
Triglycerides	99050	90.72	mg/dL	11	1.00	EUR	GLGC ¹⁰²
Renal function							
Microalbuminuria	30482	NA	log _e odds	13	0.82	EUR	CKDGen ¹⁰ ₃
Serum creatinine	67093	0.24	log _e ml/min/1.73m ²	13	1.00	EUR	CKDGen ¹⁰ ₃
Serum cystatin	20957	0.23	log _e ml/min/1.73m ²	13	1.00	EUR	CKDGen ¹⁰ ₃
Urinary albumin-to-creatinine ratio	31580	1.0	log _e mg/g	13	1.00	EUR	CKDGen ¹⁰ ₃
Other							
Grade of nuclear cataract	7140	0.8	grade	11	1.00	ASN	SEEDS ¹⁰⁴ Speliotes ¹⁰ ₅
Hepatic steatosis	7176	5.6	Hounsfield units	12	1.00	EUR	
Percent emphysema	7914	0.71	log _e %+1	12	1.00	ME	MESA ¹⁰⁶
Uric acid	42742	1.3	mg/dL	12	1.00	EUR	GUGC ¹⁰⁷

Study acronyms: CKDGen, chronic kidney disease genetics consortium; EGG, Early Growth Genetics Consortium; GIANT, Genetic Investigation of ANthropometric Traits; GUGC, Global Urate and Gout consortium; TAG, Tobacco and Genetics Consortium; ICBP, International Consortium for Blood Pressure; SSGAC, Social Science Genetics Association Consortium; MAGIC, Meta-Analyses of Glucose and Insulin-related traits Consortium; MESA, Multi-Ethnic Study of Atherosclerosis; GLGC, Global Lipids Genetics Consortium; SEEDS, the Singapore Epidemiology of Eye Diseases Study. **Abbreviations:** ASN, Asian; Con., concentration; EUR, European population; ME, multi-ethnic; SD - standard deviation; log_e, natural log; Stat., statistical

Supplementary Table S3. Selected prospective observational studies of the association between leukocyte telomere length and disease

Cohort / first author	Disease	Year	Design	No. of controls / cohort size	No. of cases	RR (95% CI) as reported by study	Scale of RR reported by study	Conversion factor [§]	RR (95% CI) per SD increase in TL	Adjusted [†]	Pop.	P _{het}	Search strategy [‡]
Cancer outcomes													
NHS, HPFS ¹⁰⁸	Bladder cancer	2007	NCC	192	184	1.88 (1.05 to 3.36)	shortest vs. longest quartile	2.54	1.28 (1.02 to 1.61)	++	EUR	NA	2
CCHS, CGPS ¹⁰⁹	Breast cancer	2013	PC	24588	574	0.99 (0.95 to 1.03)	per 1000 bp (1.29 SD) decrease	-1.29	1.01 (0.98 to 1.04)	+++++	EUR		1
SWHS ¹¹⁰	Breast cancer	2013	NCC	695	601	1.77 (1.02 to 3.06)	shortest vs. longest quintile	2.80	1.23 (1.01 to 1.49)	++	EA	0.17	2
Sister Study ¹¹¹	Breast cancer	2011	Case-cohort	735	342	0.93 (0.64 to 1.35)	shortest vs. longest quartile	-2.54	1.03 (0.89 to 1.19)	+	EUR (92%)		1
EPIC ¹¹²	Breast cancer	2010	NCC	420	199	1.58 (0.75 to 3.31)	shortest vs. longest quartile	2.54	1.2 (0.89 to 1.6)	+	EUR		1
WHS ¹¹³	Colorectal cancer	2010	NCC	357	134	0.94 (0.65 to 1.38)	per unit (1.30 SD) decrease	-1.30	1.05 (0.78 to 1.4)	+++++	EUR		3
PHS ¹¹⁴	Colorectal cancer	2009	NCC	306	191	0.8 (0.55 to 1.16)	per unit (1.72 SD) decrease	-1.72	1.14 (0.92 to 1.41)	++++	EUR		3
CCHS, CGPS ¹⁰⁹	Colorectal cancer	2013	PC	46748	496	0.97 (0.88 to 1.07)	per 1000 bp (1.29 SD) decrease	-1.29	1.02 (0.95 to 1.1)	++++	EUR	0.47	1
SWHS ¹¹⁵	Colorectal cancer	2012	NCC	549	441	1.61 (0.94 to 2.75)	longest vs. 3rd shortest quintile	1.40	1.4 (0.96 to 2.06)	+	EA		1
EPIC ¹¹²	Colorectal cancer	2010	NCC	406	185	1.13 (0.54 to 2.36)	shortest vs. longest quartile	-2.54	0.95 (0.71 to 1.27)	+	EUR		1
NHS ¹¹⁶	Endometrial cancer	2010	NCC	791	279	1.2 (0.73 to 1.96)	shortest vs. longest quartile	-2.54	0.93 (0.77 to 1.13)	+++++	EUR	0.11	2
CCHS, CGPS ¹⁰⁹	Endometrial cancer	2013	PC	25262	103	0.85 (0.71 to 1.02)	per 1000 bp (1.29 SD)	-1.29	1.13 (0.99 to 1.31)	+++++	EUR		1

													decrease	
PLCO ¹¹⁷	Glioma	2013	NCC	198	101	1.26 (0.69 to 2.29)	shortest vs. longest tertile	-2.18	0.9 (0.68 to 1.18)	++	EUR	NA	1	
CCHS, CGPS ¹⁰⁹	Head & neck cancer	2013	PC	47036	76	1.17 (0.9 to 1.53)	per 1000 bp (1.29 SD) decrease	-1.29	0.89 (0.72 to 1.09)	++++	EUR	NA	1	
CCHS, CGPS ¹⁰⁹	Kidney cancer	2013	PC	47063	59	1.04 (0.78 to 1.39)	per 1000 bp (1.29 SD) decrease	-1.29	0.97 (0.77 to 1.21)	++++	EUR	NA	1	
PLCO ¹¹⁸	Kidney cancer	2013	NCC	410	209	0.8 (0.5 to 1.5)	longest vs. shortest quartile	2.54	0.92 (0.74 to 1.14)	+++	EUR (89.5%)	NA	1	
PLCO, ATBC, SWHS ¹¹⁹	Lung adenocarcinoma	2014	NCC	288	288	2.52 (1.38 to 4.6)	longest vs. shortest quartile	2.54	1.44 (1.14 to 1.82)	++	EUR (75%)	NA	1	
CCHS, CGPS ¹⁰⁹	Lung cancer	2013	PC	47035	522	1.08 (0.98 to 1.2)	per 1000 bp (1.29 SD) decrease	-1.29	0.94 (0.87 to 1.02)	++++	EUR	<0.001	1	
PLCO, ATBC, SWHS ¹¹⁹	Lung cancer	2014	NCC	847	847	1.86 (1.33 to 2.62)	longest vs. shortest quartile	2.54	1.28 (1.12 to 1.46)	++	EUR (75%)		1	
PLCO, ATBC, SWHS ¹¹⁹	Lung SCC	2014	NCC	163	163	1.14 (0.53 to 2.45)	longest vs. shortest quartile	2.54	1.05 (0.78 to 1.42)	++	EUR (75%)		NA	1
CCHS, CGPS ¹⁰⁹	Melanoma	2013	PC	46805	177	0.89 (0.77 to 1.03)	per 1000 bp (1.29 SD) decrease	-1.29	1.09 (0.98 to 1.23)	++++	EUR	0.03	1	
WHI, HPFS, NHS ¹²⁰	Melanoma	2011	NCC	579	557	0.43 (0.27 to 0.7)	shortest vs. longest quartile	-2.54	1.39 (1.16 to 1.68)	+	EUR		2	
CCHS, CGPS ¹⁰⁹	Ovarian cancer	2013	PC	25367	96	0.85 (0.7 to 1.03)	per 1000 bp (1.29 SD) decrease	-1.29	1.13 (0.98 to 1.32)	+++++	EUR	NA	1	
CCHS, CGPS ¹⁰⁹	Pancreatic cancer	2013	PC	47091	124	1.14 (0.93 to 1.41)	per 1000 bp (1.29 SD) decrease	-1.29	0.9 (0.77 to 1.06)	++++	EUR	0.05	1	
ATBC ¹²¹	Pancreatic cancer	2013	NCC	660	193	1.58 (1.02 to 2.46)	longest vs. shortest quartile	2.54	1.2 (1.01 to 1.42)	++	EUR		1	

EPIC ¹²²	Pancreatic cancer	2014	NCC	331	331	1.38 (0.8 to 2.41)	longest vs. shortest quartile	2.54	1.13 (0.91 to 1.41)	+	EUR		1
CCHS, CGPS ¹⁰⁹	Prostate cancer	2013	PC	21387	418	0.94 (0.85 to 1.04)	per 1000 bp (1.29 SD) decrease	-1.29	1.05 (0.97 to 1.13)	++++	EUR	0.37	1
HPFS ¹²³	Prostate cancer	2015	NCC	935	922	1.11 (1.01 to 1.22)	per SD increase	1.00	1.11 (1.01 to 1.22)	++++	EUR		1
NHS ¹²⁴	Skin BCC	2011	NCC	1683	363	0.91 (0.66 to 1.25)	longest vs. shortest quartile	2.54	0.96 (0.85 to 1.09)	+	EUR	NA	1
CCHS, CGPS ¹⁰⁹	Testicular cancer	2013	PC	21568	10	1.09 (0.57 to 2.09)	per 1000 bp (1.29 SD) decrease	-1.29	0.94 (0.56 to 1.55)	++++	EUR	NA	1
Non-neoplastic diseases													
Haycock ¹¹¹²⁵	Coronary heart disease	2014	MA	27352	2272	1.4 (1.15 to 1.7)	shortest vs. longest tertile	-2.18	0.86 (0.78 to 0.94)	*	EUR	NA	4
Haycock ^{#125}	Ischemic stroke	2014	MA	5300	824	1.14 (0.85 to 1.54)	shortest vs. longest tertile	-2.18	0.94 (0.82 to 1.08)	*	EUR	NA	4
Bruneck, SHFS, WHI ¹²⁶	Type 2 diabetes	2014	MA	6991	2011	1.31 (1.07 to 1.6)	shortest vs. longest quartile	-2.54	0.9 (0.83 to 0.97)	**	Mix	NA	4

†Search strategy used to identify the study (see Table S4 for details). ‡Meta-analysis of 11 prospective studies; §Meta-analysis of 6 prospective studies (90% of cases were ischemic stroke, 10% were unclassified cerebrovascular disease); ¶To convert reported log RR to log RR per SD increase in telomere length; †Adjustment for confounders: +adjusted for age and sex; ++plus smoking; +++plus body mass index; ++++plus alcohol and/or physical activity; +++++plus hormone replacement therapy, menopause and/or parity; *most studies adjusted for age, sex and non-lipid vascular risk factors; **adjusted for age, sex and body mass index.

Acronyms/abbreviations: BCC, basal cell carcinoma; bp, base pairs; CI, confidence interval; EA, East Asian; EUR, European; MA, random-effects meta-analysis of prospective studies; NCC, nested case-control study; PC, prospective cohort; Phet, p value for heterogeneity between studies; Pop., population; RR, relative risk; SD, standard deviation; SCC, squamous cell carcinoma; vs., versus; TL, telomere length. **Study acronyms:** ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; EPIC, European Prospective Investigation into Cancer and Nutrition study; HPFS, Health Professionals Follow-Up Study; NHS, Nurses Health Study; PHS, Physicians' Health Study; PLCO, Prostate, Lung, Colorectal, and Ovarian; SHFS, Strong Heart Family Study; the Sister Study; SWHS, Shanghai Women's Health Study; WHI, Women's Health Initiative; WHS, Women's Health Study

Supplementary Table S4. PubMed search strategy for prospective observational studies of association between telomere length* and disease

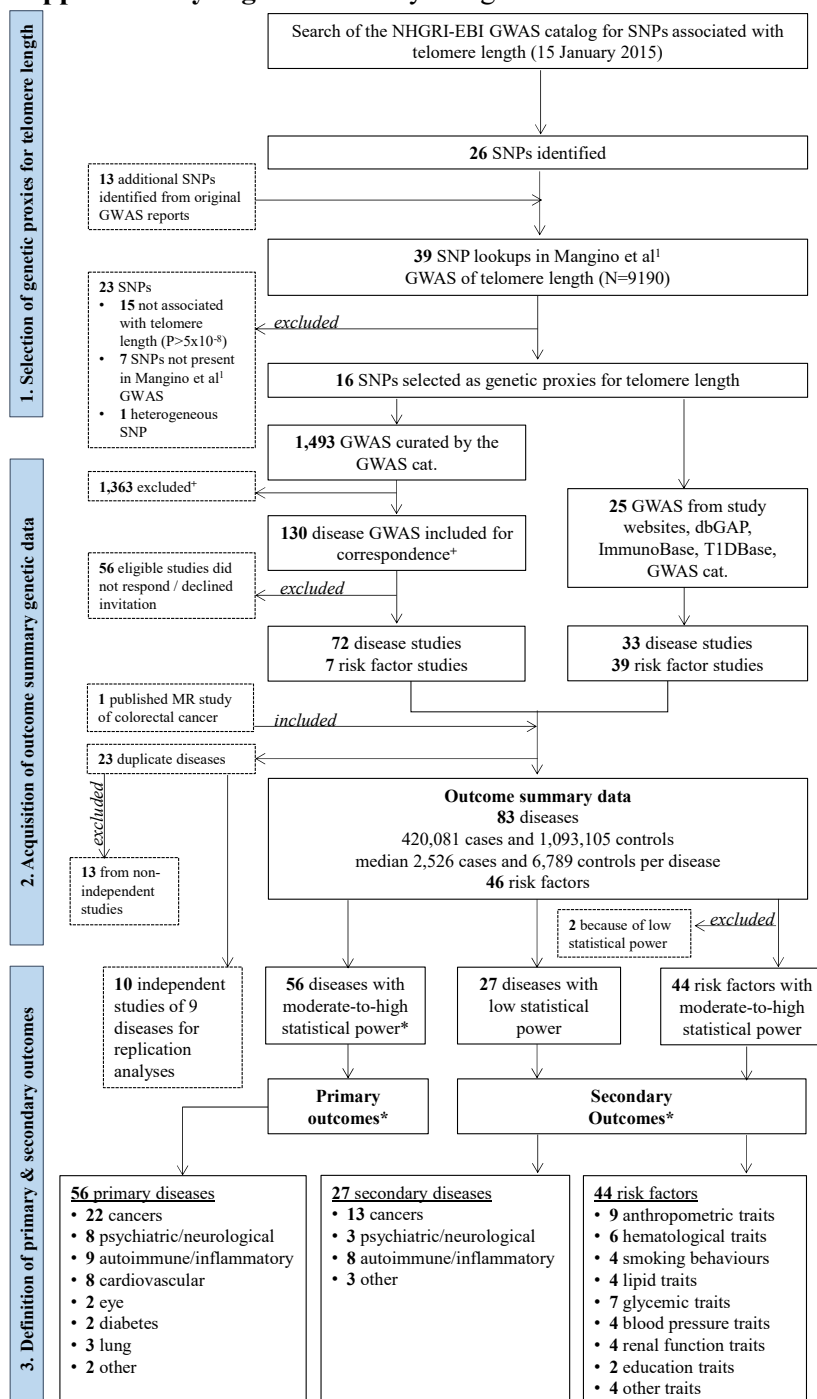
Search strategy	Search terms or meta-analysis	No. of studies identified	No. meeting inclusion criteria	Reasons for further exclusions	No. of studies included
<i>Inclusion criteria: prospective study of primary cancer outcome and telomere length[†]</i>					
Strategy 1	25 February 2015: cancer[TIAB] AND telomere length[TIAB] AND (meta analysis[TIAB] OR prospective[TIAB] OR meta-analysis[TIAB]) 25 March 2015: telomere length[Title/Abstract] AND (retrospective[Title/Abstract] OR case-control[Title/Abstract] OR case control[Title/Abstract] OR meta-analysis[Title/Abstract] OR meta analysis[Title/Abstract] OR prospective[Title/Abstract] OR cohort[Title/Abstract] OR cross-sectional[Title/Abstract] OR cross sectional[Title/Abstract]) AND (B-cell non-Hodgkin lymphoma[Title/Abstract] OR breast cancer[Title/Abstract] OR chronic myeloid leukemia[Title/Abstract] OR esophageal adenocarcinoma[Title/Abstract] OR endometrial cancer[Title/Abstract] OR esophageal cancer[Title/Abstract] OR gastric cancer[Title/Abstract] OR gallbladder cancer[Title/Abstract] OR glioma[Title/Abstract] OR head cancer[Title/Abstract] OR neck cancer[Title/Abstract] OR oesophageal adenocarcinoma[Title/Abstract] OR kidney cancer[Title/Abstract] OR melanoma[Title/Abstract] OR nasopharyngeal carcinoma[Title/Abstract] OR neuroblastoma[Title/Abstract] OR non-melanoma skin cancer[Title/Abstract] OR basal cell carcinoma[Title/Abstract] OR squamous cell carcinoma[Title/Abstract] OR ovarian cancer[Title/Abstract] OR pancreatic cancer[Title/Abstract] OR prostate cancer[Title/Abstract] OR testicular germ cell cancer[Title/Abstract] OR Wilm's tumour[Title/Abstract] OR Bladder cancer[Title/Abstract] OR Breast cancer[Title/Abstract] OR Chronic lymphocytic leukemia[Title/Abstract] OR Colorectal cancer[Title/Abstract] OR Multiple myeloma[Title/Abstract] OR Lung adenocarcinoma[Title/Abstract] OR Lung squamous cell cancer[Title/Abstract] OR cancer[Title/Abstract] OR osteosarcoma[Title/Abstract] OR leukemia[Title/Abstract] OR leukaemia[Title/Abstract] OR Ewing sarcoma[Title/Abstract])	54	11	NA	11 [‡]
Strategy 2		209	17	13 duplicates	4
Strategy 3	Ma et al ¹²⁷ (2011) and Wentzensen et al ¹²⁸ (2011)	48	10	8 duplicates	2
<i>Inclusion criteria: prospective study of primary disease outcome and telomere length[†]</i>					
Strategy 4	8 January 2016: (meta-analysis OR "meta analysis") AND "telomere length"	42	7	2 did not report relative risks [§] ; 3 duplicates	2

*all identified eligible studies were studies of leukocyte telomere length; [†]1 study reported findings for 2 primary cancer outcomes and 1 study reported findings for 11 primary cancer outcomes; ^{||}1 meta-analysis reported findings for 2 primary non-neoplastic diseases; [‡]primary outcomes were diseases where a priori statistical power was >50% to detect associations with telomere length (see supplementary text for technical details); see table S1 for a list of the primary disease outcomes; [§]relative risks were defined as odds ratios, hazard ratios and risk ratios

Supplementary Table S6. Glossary of terms

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Mendelian randomization	A technique to appraise causality in observational studies using genetic variants as ‘unconfounded’ instruments for risk factors or modifiable exposures of interest.
Instrumental variable	A ‘proxy’ variable used in place of the hypothesized risk factor or exposure in a Mendelian randomization analysis. A valid instrumental variable is associated with the exposure of interest but is not associated with confounders; and is associated with the outcome (e.g. disease) exclusively via its effect on the hypothesized exposure (see Supplementary Figure S7 for an illustration of these assumptions).
Reverse causation	When the outcome causes variation in the hypothesized exposure and not <i>vice versa</i> .
Confounding	When the association between exposure and outcome is not due to a causal relationship between the two variables but arises as a result of the separate effects of a third variable (the confounder) on the exposure and the outcome. Mendelian randomization studies are less susceptible to confounding in comparison to observational studies (but confounding by pleiotropy or population stratification is possible).
Pleiotropy	Occurs when a genetic variant is associated with multiple traits or phenotypes. Vertical pleiotropy occurs when the phenotypes are on the same causal pathway (and is less problematic for Mendelian randomization studies). Horizontal pleiotropy occurs if the phenotypes are associated with the genetic variant via separate pathways and can introduce confounding into a Mendelian randomization analysis. Sensitivity analyses, such as MR-Egger, the weighted median, scatter plots and funnel plots, can be used to test and, in some instances, adjust for pleiotropy.
Collider bias	The phenomenon by which statistical adjustment for a variable, M (known as the collider), that is a downstream consequence of both the exposure X and the outcome Y, induces an association between X and Y that was not previously present, and therefore leads to bias. In MR, if published genetic associations with the exposure and/or outcome are adjusted for a collider, this may lead to collider bias.
Weak instrument bias	Occurs when the instrument is only weakly associated with the exposure. Can introduce confounding into a Mendelian randomization analysis when the exposure and outcome data come from the same sample. When exposure and outcome data come from separate samples, as in two-sample Mendelian randomization, bias is towards the null. An F statistic > 10, for the association between the instrument and exposure, is sometimes used as a threshold for defining strong instruments, although weak instrument bias varies continuously with the strength of the F statistic.

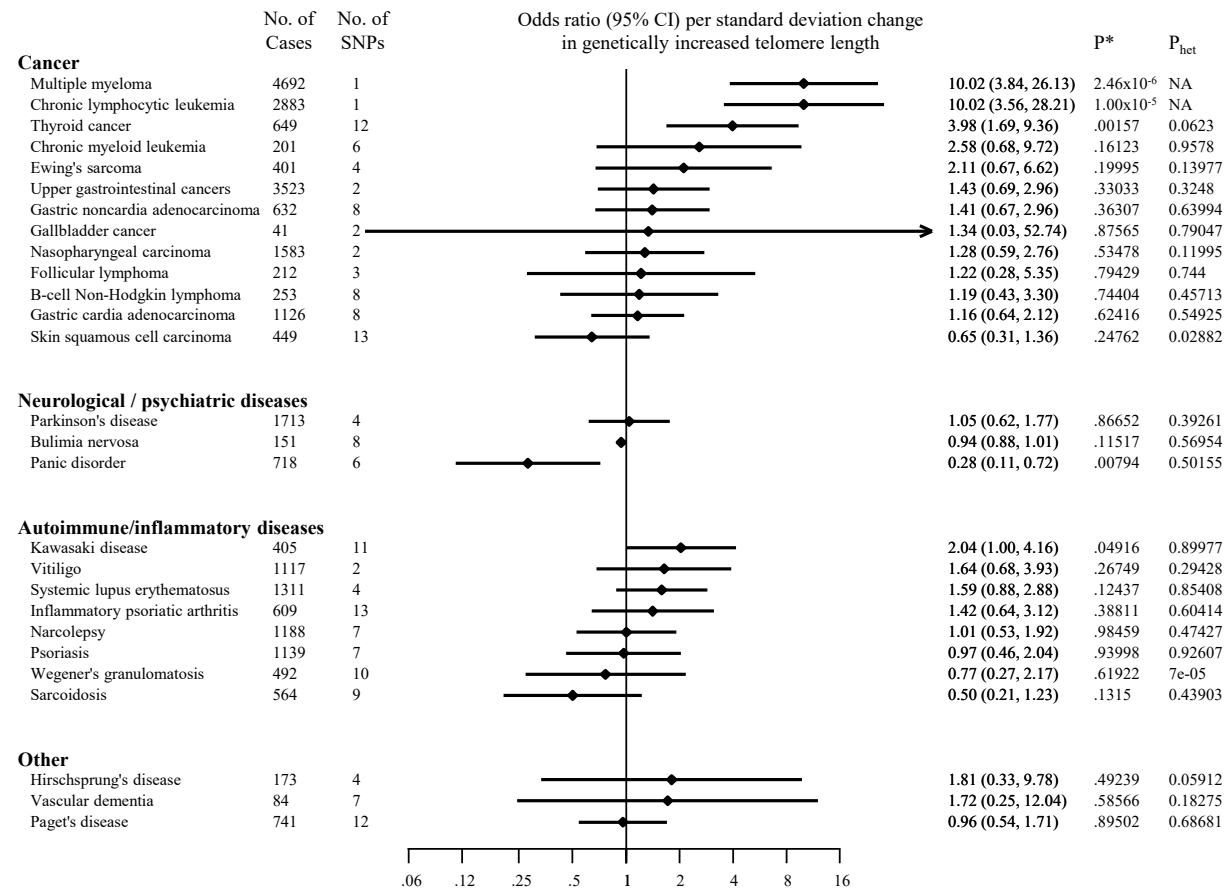


+We searched the GWAS catalog in January 2015 for studies of non-communicable diseases that did not select controls on the basis of pre-existing conditions. Of the 1493 studies in the GWAS catalog with unique PubMed reference numbers, we classified 773 as disease studies (the excluded non-disease studies were typically studies of risk factors for disease, biomarkers or response to treatments). A further 103 studies were excluded for the following reasons: studies of infectious diseases, studies of congenital abnormalities, studies of (not-cause specific) mortality, studies nested within disease populations and studies using pooled DNA samples. Of the 670 remaining non-communicable disease studies, 130 were identified for correspondence. Our objective was to obtain the single largest available study for each non-communicable disease, so as to avoid unnecessary correspondence with duplicate studies and to avoid including studies with overlapping samples.

*Primary outcomes were diseases with sufficient cases and controls for >50% power and secondary outcomes were diseases with <50% power to detect odds ratios ≥ 2.0 per standard deviation change in genetically increased telomere length (alpha assumed to be 0.01). All risk factors were classified as secondary outcomes. **GWAS**, genome-wide association study; **GWAS Cat.**, NHGRI-EBI GWAS catalogue; **SNP**, single nucleotide polymorphism; **NHGRI**, National Human Genome Research Institute; **EBI**, European Bioinformatics Institute

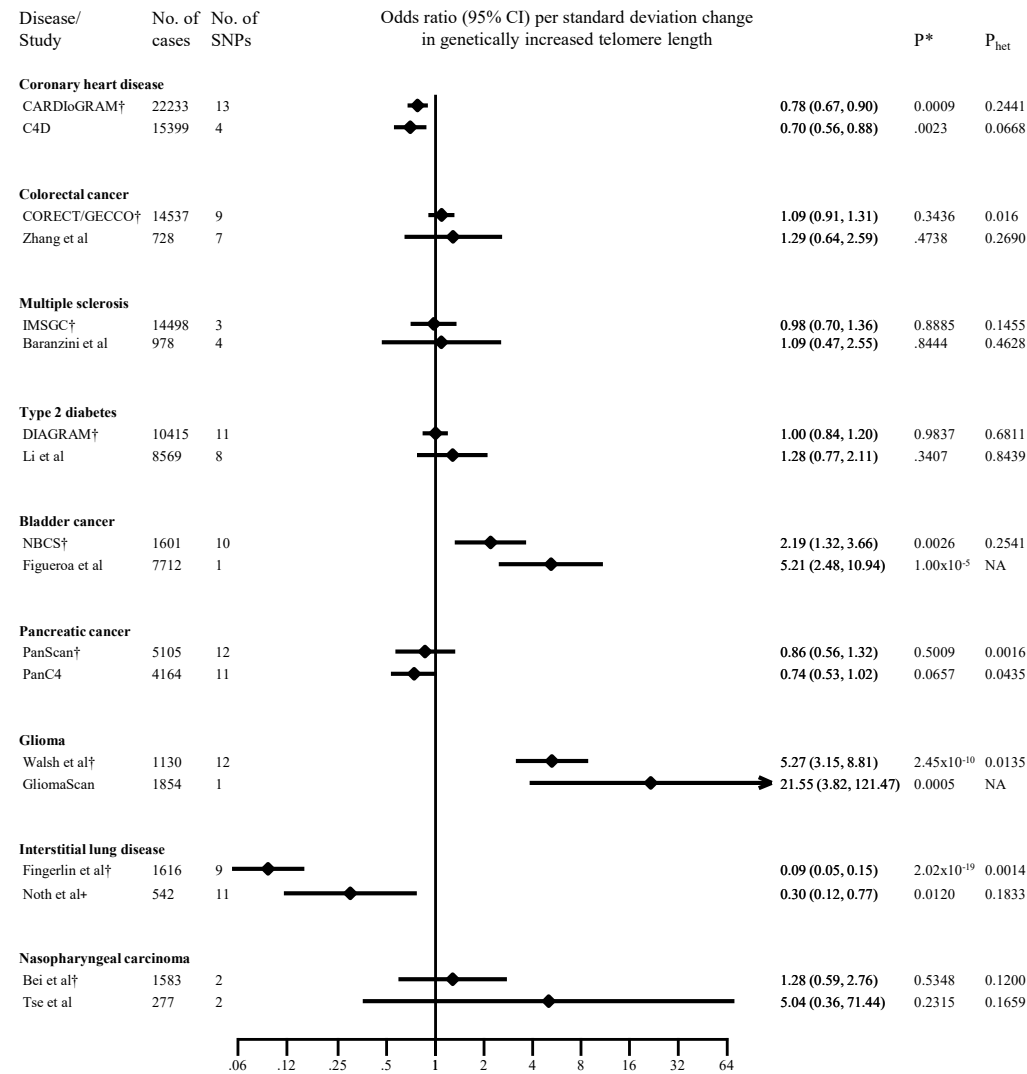
336 | **Supplementary Figure S2.** Association between genetically increased telomere length and odds of secondary non-communicable diseases

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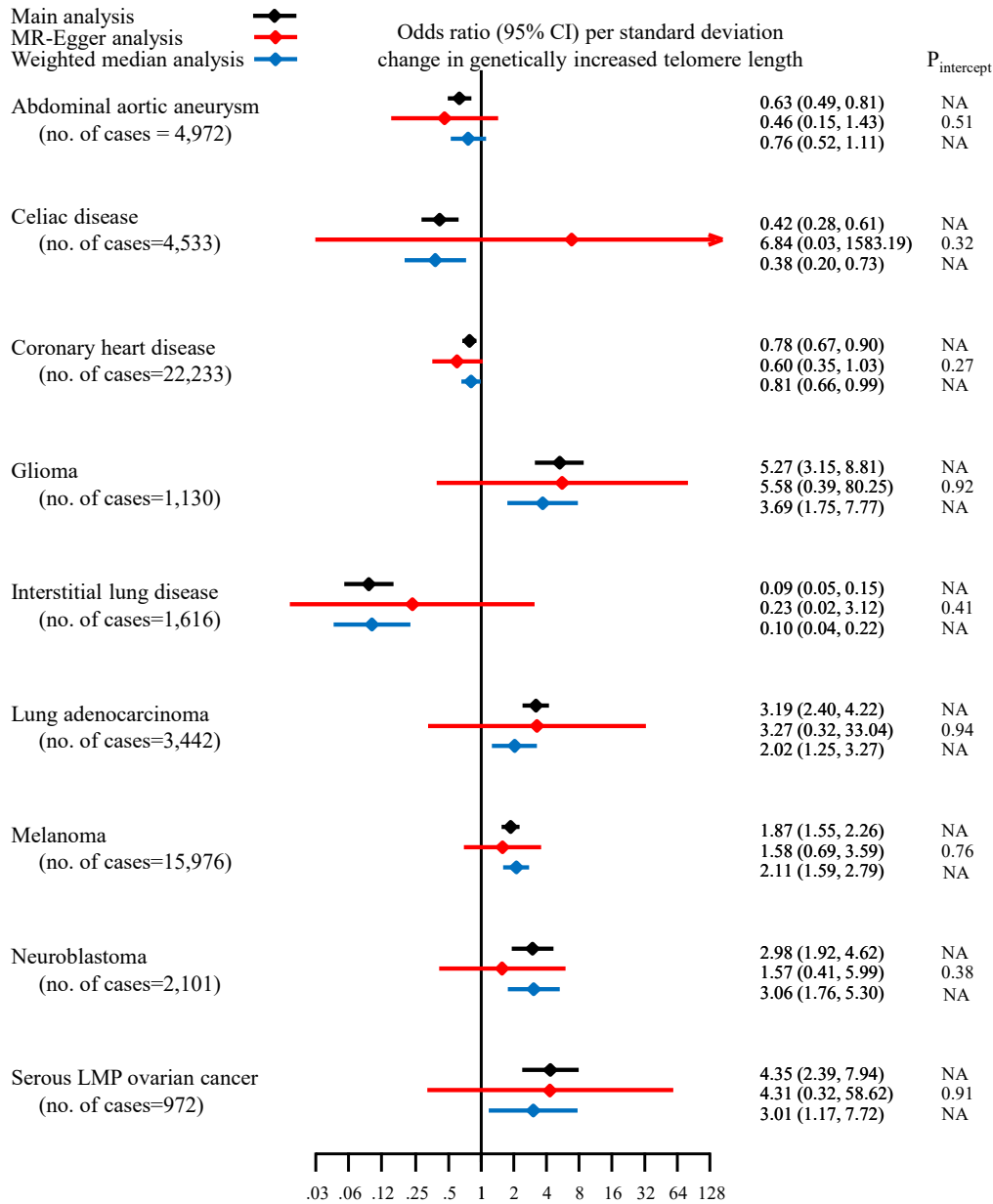
337 *P value for association between genetically increased telomere length and disease from maximum likelihood; P_{het}, P value for heterogeneity amongst SNPs within the genetic risk score; SNP, single
338 nucleotide polymorphism; CI, confidence interval
339

Supplementary Figure S3. Replication of association between genetically increased telomere length and odds of non-communicable diseases in independent datasets



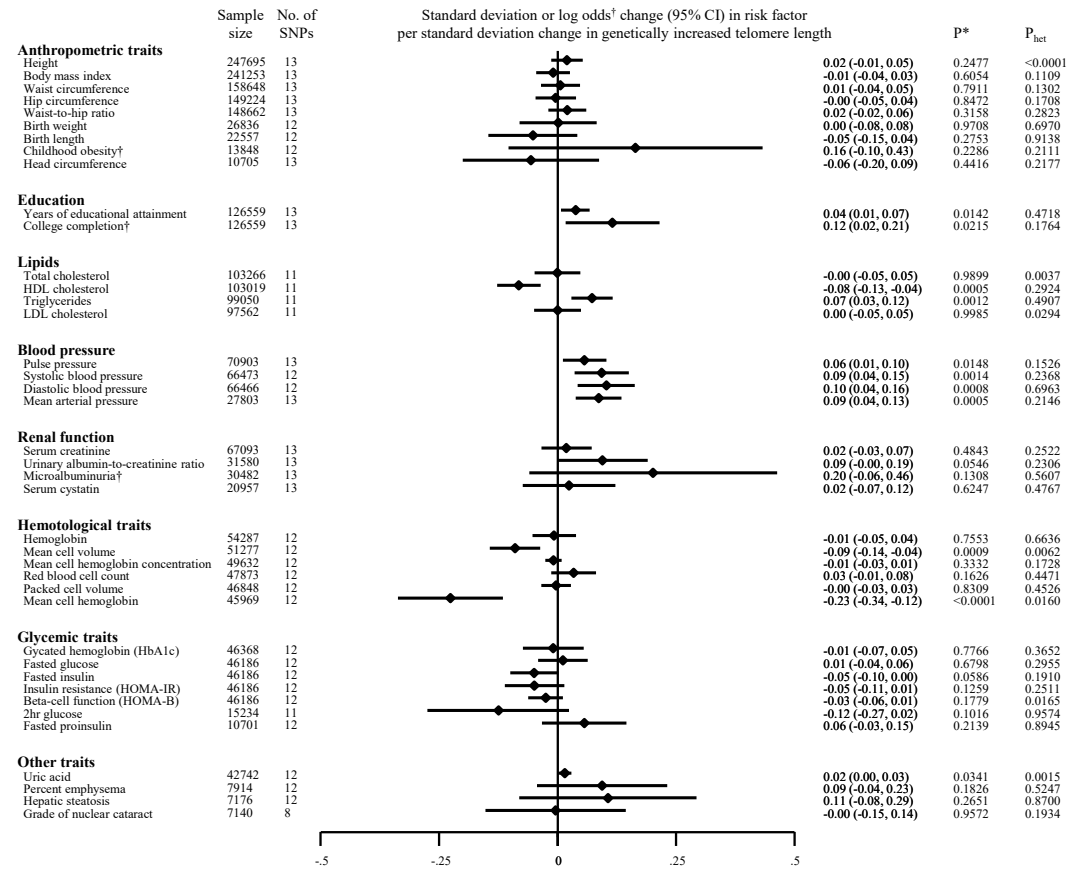
*P value for association between genetically increased telomere length and disease from maximum likelihood. †Primary or secondary study from Fig. 1 or Fig. S2. ‡Noth et al³¹: ≤17% of the cases overlapped with cases from Fingerlin et al³¹ and 77% of cases had idiopathic pulmonary fibrosis; ‡An inverse association was also observed in Mushirola et al³². P_{het}, p value for heterogeneity amongst SNPs in the genetic risk score (NA when only a single SNP available); SNP, single nucleotide polymorphism; CI, confidence interval. **Study abbreviations:** C4D, Coronary Artery Disease Genetics Consortium; CARDIoGRAM, Coronary Artery Disease Genome wide Replication and Meta-analysis; CORECT, ColoRectal Transdisciplinary Study; GECCO, Genetics and Epidemiology of Colorectal Cancer Consortium; IMSGC, International Multiple Sclerosis Genetic Consortium; NBCS, Nijmegen Bladder Cancer Study; IMSGC, International Multiple Sclerosis Genetic Consortium.

355 **Supplementary Figure S4.** Sensitivity analyses of association between genetically increased
356 telomere length and odds of non-communicable diseases
357



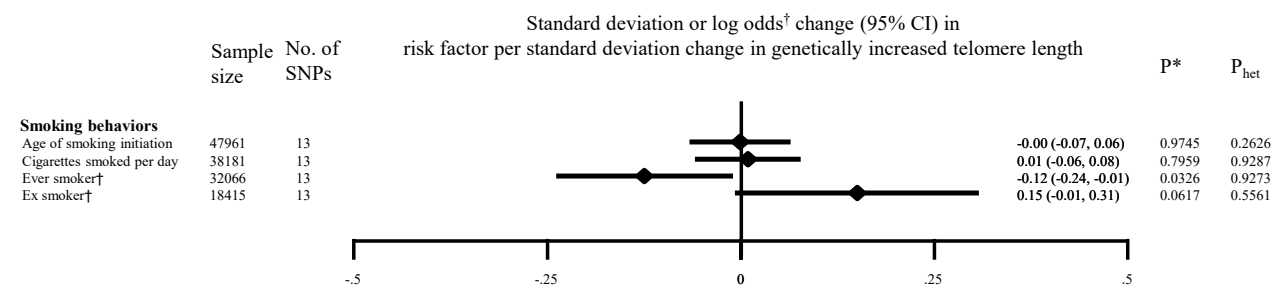
358 LMP, low malignancy potential; CI, confidence interval. The $P_{\text{intercept}}$ from MR-Egger regression tests the null hypothesis that the
359 intercept is zero and can be interpreted as a statistical test for the presence of directional (bias inducing) pleiotropy; the smaller the
360 $P_{\text{intercept}}$ value the stronger the evidence for directional pleiotropy.
361

Supplementary Figure S5. Association between genetically increased telomere length and risk factors for non-communicable diseases



*P value for association between genetically increased telomere length and risk factor from maximum likelihood; P_{het}, p value for heterogeneity amongst SNPs within the genetic risk score; SNP, single nucleotide polymorphism; CI, confidence interval; HbA1c, hemoglobin A1c; HOMA-B, homeostatic model assessment β -cell function; IR, insulin resistance; †for binary risk factors results reflect the log odds ratio for the risk factor, all other results reflect the standard deviation change in the risk factor

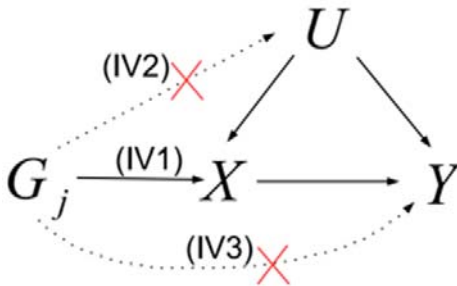
363 **Supplementary Figure S6.** Association between genetically increased telomere length and smoking



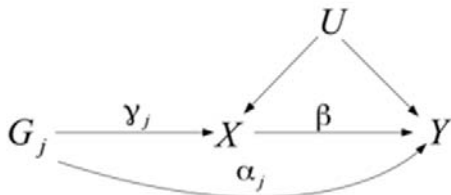
*P value for association between genetically increased telomere length and risk factor from maximum likelihood; P_{het}, P value for heterogeneity amongst SNPs within the genetic risk score; SNP, single nucleotide polymorphism; CI, confidence interval; [†]for binary risk factors results reflect the log odds ratio for the risk factor, all other results reflect the standard deviation change in the risk factor

Supplementary Figure S7. Causal diagram illustrating the assumptions of Mendelian randomization

a)



b)



IV, instrumental variable assumption; G_j , single nucleotide polymorphism j ; X , telomere length; Y , outcome (disease or risk factor); U , confounder; α , G - Y association not mediated by telomere length (often described as a horizontal pleiotropic or direct effect); γ , SNP-telomere-length association.

a) Key assumptions of Mendelian randomization. G_j is associated with X (IV1); G_j is independent of confounders (IV2); G_j is independent of Y given X and U (IV3). The weighted median approach assumes that IV1-IV3 hold for genetic variants making up at least 50% of the weight in the analysis; MR-Egger relaxes assumption IV3 (see InSIDE assumption below).

b) Assumptions underlying the MR-Egger approach. IV3 is replaced with the InSIDE assumption (Instrument Strength Independent of Direct Effect): the strength of the pleiotropic effect (α_j) does not correlate with the strength of the G - X association (γ_j). Under the InSIDE assumption, MR-Egger can consistently estimate the causal effect of X on Y , represented by the parameter β in (b).

392 **ACKNOWLEDGEMENTS OF THE CONTRIBUTING STUDIES AND CONSORTIA**

393

394 **Amyotrophic lateral sclerosis GWAS consortium**

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410 *Funding/Support*

411 I. Fogh was supported by funds from Motor Neurone Disease Association of Great Britain and
412 Northern Ireland (grant n.905-793, 6058).

413 J.Powell, A.Al-Chalabi and I.Fogh received salary support from the National Institute for Health

414 Research (NIHR) Dementia Biomedical Research Unit at South London and Maudsley NHS

415 Foundation Trust and King's College London. The UK National DNA Bank for MND Research was

416 funded by the Motor Neurone Disease Association (grant 3/3), the Wellcome Trust (grant

070122/A/02/Z) and the NIHR Dementias and Neurodegenerative Diseases Research Network (DeNDRoN).

V. Silani was supported by Agenzia Italiana per la Ricerca sulla SLA-AriSLA (grant NOVALS 2012 cofinanced with the contribution of 5 x 1000, Healthcare Research support of the Ministry of Health), the Italian Ministry of Health (Grant ALS-FTD, Ric. Finalizzata 2009 no.276) and Associazione Amici “Centro Dino Ferrari”.

J.H. Veldink was supported by the Netherlands Organisation for Health Research and Development.

The Aneurysm Consortium

GWAS data on abdominal aortic aneurysm (AAA) studies

All known studies with AAA genome-wide genotyping were invited to join the International Aneurysm Consortium. All studies agreed to participate in the meta-GWAS, with cohort case control descriptions and inclusion/exclusion criteria having been previously reported.^{28,129,130} All AAA cases shared a common definition of infra-renal aortic diameter >30 mm.

Descriptions of AAA cohorts

In the present report, the Aneurysm Consortium consists of the original Aneurysm Consortium plus the NZ AAA Genetics Study (two separate cohorts), the Geisinger Vascular Clinic AAA study, the Iceland study and the Netherlands study.

Original Aneurysm Consortium (1846 cases and 5605 controls): The original Aneurysm Consortium recruited cases of AAA from centres across the United Kingdom and Western Australia. Cases were defined as an infra-renal aortic diameter \geq 30 mm proven on ultrasound or computerized tomography (CT) scan. Controls were taken from the WTCCC2 common control group^{28,131} and were therefore unscreened for AAA.

NZ AAA Genetics Study (with two separate cohorts: set 1 with 608 cases and 612 controls; set 2 with 397 cases and 384 controls): The Vascular Research Consortium of New Zealand recruited

443 New Zealand men and women with a proven history of AAA (infra-renal aortic diameter \geq 30 mm
444 proven on ultrasound or CT scan). Approximately 80% had undergone surgical AAA repair
445 (typically AAA's > 50-55 mm in diameter). The vast majority of cases (>97%) were of Anglo-
446 European ancestry. The control group underwent an abdominal ultrasound scan to exclude (>25
447 mm) concurrent abdominal aortic aneurysm and Anglo-European ancestry was required for
448 inclusion. Controls were also screened for peripheral artery disease (PAD; using ankle brachial
449 index), carotid artery disease (ultrasound) and other cardiovascular risk factors.

450

451 Geisinger Vascular Clinic AAA Study, Pennsylvania, USA: AAA patients (n=724) were enrolled
452 through the Department of Vascular Surgery at Geisinger Medical Center, Danville, PA. Details of
453 this case-control set have been reported previously, and the samples have been used in previous
454 association studies.^{129,132} To identify cases and controls from the electronic medical records, an
455 ePhenotyping algorithm was developed²⁹. AAA cases were defined as infrarenal aortic diameter \geq
456 30 mm as revealed by abdominal imaging. Approximately 20% of individuals with AAA had a
457 family history of AAA. A control group (n=1231) was obtained through the Geisinger MyCode®
458 Project, a cohort of Geisinger Clinic patients recruited for genomic studies. The MyCode® controls
459 were matched for age distribution and sex to the Geisinger Vascular Clinic AAA cases. Based on
460 electronic medical records, controls had no ICD-9 codes for AAA in their records, but they were
461 not screened by ultrasonography for AAA. Both cases and controls from the Geisinger Clinic were
462 of European descent. The eMERGE Network Imputed GWAS for 41 Phenotypes (the dbGaP
463 eMERGE Phase 1 and 2 Merged data Submission) accession number is: phs000888.v1.p1 which
464 includes the Geisinger AAA data.

465

466 Iceland, deCODE Genetics: Icelandic individuals with AAA (defined as infra-renal aortic diameter
467 \geq 30 mm) were recruited from a registry of individuals who were admitted at Landspítali University
468 Hospital, in Reykjavik, Iceland, 1980 – 2006. AAA patients were either followed up or treated by

469 intervention for emergency repair of symptomatic or ruptured AAA or for an elective repair by
470 surgery or endovascular intervention. In total, whole genome data from 557 subjects with AAA,
471 enrolled as part of the CVD genetics program at deCODE, were included in the metaGWAS. The
472 Icelandic controls used (n=89,235) were selected from among individuals who have participated in
473 various GWA studies and who were recruited as part of genetic programs at deCODE. Individuals
474 with known cardiovascular disease were excluded as controls¹²⁹ but controls were unscreened for
475 AAA.

476

477 The Netherlands: The AAA sample set from Utrecht was recruited in 2007-2009 from eight centres
478 in The Netherlands¹²⁹, mainly when individuals visited their vascular surgeon in the polyclinic or, in
479 rare cases, during hospital admission for elective or emergency AAA surgery. An AAA was defined
480 as an infrarenal aorta ≥ 30 mm. The sample set (n=840) comprised 89.9% males, with a mean AAA
481 diameter of 58.4 mm, 61.7% had received surgery, of which 8.1 % was after rupture. The Dutch
482 controls (n=2791) used in the AAA GWAS were recruited as part of the Nijmegen Biomedical
483 Study and the Nijmegen Bladder Cancer Study (see <http://dceg.cancer.gov/icbc/membership.html>).

484

485 *Meta-analysis of AAA GWASs*

486 Data from the six cohorts detailed above, comprising 4972 AAA cases and 99,858 controls, that
487 were genotyped with a variety of genome-wide SNP arrays. All cohorts underwent quality control
488 filtering using the manufacturers' array-specific guidelines but with consistently applied inclusion
489 criteria of SNP or sample call rates $>95\%$ and Hardy-Weinberg equilibrium $P > 5 \times 10^{-5}$ in
490 controls.^{28,129,130,132} Each cohort then underwent imputation (Impute 2.2) to a shared reference panel
491 from the 1000 Genomes project (Phase I integrated variant set release (v3), March 2012, NCBI
492 build 37(hg19) Following imputation SNPs were quality controlled by quality score ($Q > 0.9$) and
493 minor allele frequency ($MAF > 0.05$ in controls) filtering, resulting in a common set of 5331120
494 SNPs across all discovery phase participants.

495 The metaGWAS analysis was conducted using the METAL software package¹³³ on the
496 BCISNPmax database platform (version 3.5, BCI Platforms, Espoo, Finland). METAL was
497 implemented using the sample size scheme with weighting for each cohort being two times the case
498 number. The analysis was adjusted for genomic inflation (λ) in each cohort.

499

500 *Acknowledgements on AAA GWAS studies:*

501 Data provided by the original Aneurysm Consortium was funded by the Wellcome Trust (award
502 number 084695) and made use of data generated by the WTCCC. A full list of the investigators
503 who contributed to the generation of the data is available from www.wtccc.org.uk. Funding for the
504 WTCCC project was provided by the Wellcome Trust under award 076113 and 085475. Funding
505 for the New Zealand project was provided by the Health Research Council of New Zealand (08-75,
506 14-155). The Geisinger sample collection was funded in part by the Pennsylvania Commonwealth
507 Universal Research Enhancement program, the Geisinger Clinical Research Fund, the American
508 Heart Association, and the Ben Franklin Technology Development Fund of Pennsylvania. The
509 generation and management of GWAS genotype data for the Rotterdam Study (control samples for
510 the Dutch GWAS) is supported by the Netherlands Organization of Scientific Research NWO
511 Investments (nr. 175.010.2005.011, 911-03-012). This study is funded by the Research Institute for
512 Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/NWO
513 project nr. 050-060-810.

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542 **Coronary ARtery DIsease Genome wide Replication and Meta-analysis (CARDIoGRAM)**
543 **consortium and The Coronary Artery Disease (C4D) Genetics consortium**

544 We thank the CARDIoGRAM and C4D consortia for making summary data available to the
545 research community. Data on coronary artery disease / myocardial infarction have been contributed
546 by CARDIoGRAMplusC4D investigators and have been downloaded from

547 www.CARDIOGRAMPLUSC4D.ORG. The investigators within CARDIoGRAM and C4D did not
548 participate in the analysis, writing or interpretation of this report.

549

550 **The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) – Heart**
551 **Failure Working Group**

552 For a full list of CHARGE – Heart Failure working group members contributing to this work and
553 for CHARGE – Heart Failure acknowledgements please see PMID 20445134.

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590 **The Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPDGene)**

591 The COPDGene project was supported by Award Number R01HL089897 and Award Number

592 R01HL089856 from the National Heart, Lung, and Blood Institute. The content is solely the

593 responsibility of the authors and does not necessarily represent the official views of the National

594 Heart, Lung, and Blood Institute or the National Institutes of Health. The COPDGene project is

595 also supported by the COPD Foundation through contributions made to an Industry Advisory Board

596 comprised of AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Siemens, Sunovion, and

597 GlaxoSmithKline.

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667 Summary data on birth anthropometrics has been contributed by the EGG Consortium and has been
668 downloaded from www.egg-consortium.org. The investigators within the EGG did not participate in
669 the analysis, writing or interpretation of this paper.
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882 L.Paternoster is supported by an MRC Population Health Scientist Fellowship (MR/J012165/1).

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936 **Glioma GWAS**

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938 Work at University of California, San Francisco was supported by the National Institutes of Health
939 (grant numbers R01CA52689, P50CA097257, R01CA126831, R01CA139020 and
940 R25CA112355), as well as the National Brain Tumor Foundation, the Stanley D. Lewis and
941 Virginia S. Lewis Endowed Chair in Brain Tumor Research, the Robert Magnin Newman Endowed
942 Chair in Neuro-oncology, and by donations from families and friends of John Berardi, Helen
943 Glaser, Elvera Olsen, Raymond E. Cooper, and William Martinusen.

944

945 The collection of cancer incidence data used in this study was supported by the California
946 Department of Public Health as part of the statewide cancer reporting program mandated by
947 California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance,
948 Epidemiology and End Results Program under contract HHSN261201000140C awarded to the
949 Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the
950 University of Southern California, and contract HHSN261201000034C awarded to the Public
951 Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer
952 Registries, under agreement # U58DP003862-01 awarded to the California Department of Public
953 Health. The ideas and opinions expressed herein are those of the author(s) and endorsement by the
954 State of California Department of Public Health, the National Cancer Institute, and the Centers for
955 Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should
956 be inferred.

957

958 The results published here are in whole or part based upon data generated by The Cancer Genome
959 Atlas managed by the NCI and NHGRI. Information about TCGA can be found
960 at <http://cancergenome.nih.gov>

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996

997 *Funding*

998 *QIMR*: The QIMR study was supported by grants from the National Health and Medical Research
999 Council (NHMRC) of Australia (241944, 339462, 389927, 389875, 389891, 389892, 389938,
1000 443036, 442915, 442981, 496610, 496739, 552485 and 552498), the Cooperative Research Centre
1001 for Discovery of Genes for Common Human Diseases (CRC), Cerylid Biosciences (Melbourne) and
1002 donations from N. Hawkins and S. Hawkins. D.R.N. was supported by the NHMRC Fellowship
1003 (339462 and 613674) and Australian Research Council (ARC) Future Fellowship (FT0991022)
1004 schemes. S.M. was supported by NHMRC Career Development Awards (496674 and 613705).
1005 E.G.H. (631096) and G.W.M. (339446 and 619667) were supported by the NHMRC Fellowship
1006 scheme. The HCS was funded by the University of Newcastle, the Gladys M Brawn Fellowship
1007 scheme and the Vincent Fairfax Family Foundation in Australia. *OX*: The work presented here was

supported by a grant from the Wellcome Trust (WT084766/Z/08/Z) and makes use of Wellcome Trust Case Control Consortium 2 (WTCCC2) control data generated by the WTCCC. A full list of the investigators who contributed to the generation of these data is available at the Wellcome Trust website (<http://www.wtccc.org.uk/>). Funding for the WTCCC project was provided by the Wellcome Trust under awards 076113 and 085475. C.A.A. was supported by a grant from the Wellcome Trust (098051). A.P.M. was supported by a Wellcome Trust Senior Research Fellowship. S.H.K. is supported by the Oxford Partnership Comprehensive Biomedical Research Centre, with funding from the Department of Health National Institute for Health Research (NIHR) Biomedical Research Centres funding scheme. K.T.Z. is supported by a Wellcome Trust Research Career Development Fellowship (WT085235/Z/08/Z). **BBJ:** We thank the members of the Rotary Club of Osaka-Midosuji District 2660 Rotary International in Japan for supporting our study. This work was conducted as part of the BioBank Japan Project that was supported by the Ministry of Education, Culture, Sports, Science and Technology of the Japanese government.

1021

European Periodontitis Genetics Group (EPG)

The GWAS of aggressive periodontitis (AgP) was supported by a research grant of the Deutsche Forschungsgemeinschaft DFG (GZ: SCHA 1582/3-1). The cohort case description has been previously reported in Schaefer A.S. *et al.* Genetic evidence for PLASMINOGEN as a shared genetic risk factor of coronary artery disease and periodontitis. *Circ Cardiovasc Genet* **8**, 159-67 (2015). The investigators who contributed to the generation of this case sample are: Henrik Dommisch¹, Christian Graetz², Inga Harks³, Yvonne Jockel-Schneider⁴, Jörg Eberhardt⁵, Joerg Meyle⁶, Peter Eickholz⁷, Mathias Folwaczny⁸, Barbara Noack⁹, Wolfgang Lieb¹⁰, Christof Doerfer², Corinna Bruckmann¹¹, Søren Jepsen¹²

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1054 Genotyping of the AgP cases was performed on an IScan system with HumanOmni BeadChips
1055 (Illumina) at the Institute of Clinical Molecular Biology, Christian-Albrechts-University Kiel,
1056 Germany. We specially thank Andre Franke and Stefan Schreiber.

1057 The aggressive periodontitis control sample consists of three independent studies:

1058 1. The Heinz-Nixdorff-Recall (HNR) was described in Schmermund, A., *et al.* Assessment of
1059 clinically silent atherosclerotic disease and established and novel risk factors for predicting

1060 myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the
1061 Heinz Nixdorf RECALL Study. Risk Factors, Evaluation of Coronary Calcium and Lifestyle. *Am*
1062 *Heart J* **144**, 212-18 (2002). The HNR study was supported by the Heinz Nixdorf Foundation
1063 (Germany). Additionally, the study was funded by the German Ministry of Education and Science
1064 and the German Research Council (DFG; Project SI 236/8-1, SI236/9-1, ER 155/6-1). The
1065 genotyping of the Illumina HumanOmni-1 Quad BeadChips of the HNR subjects was financed by
1066 the German Centre for Neurodegenerative Disorders (DZNE), Bonn. We are extremely grateful to
1067 all investigators who contributed to the generation of this dataset.

1068 The HNR study is represented by Per Hoffmann^{1,2} and Bastian Krone³

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1075 2. The Dortmund Health Study (DOGS) is described in Berger, K. *et. al.* DHS: The Dortmund
1076 health study. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz* **55**, 816-21 (2012).
1077 DOGS is supported by the German Migraine & Headache Society (DMKG) and by unrestricted
1078 grants of equal share from Almirall, Astra Zeneca, Berlin Chemie, Boehringer, Boots Health Care,
1079 Glaxo-Smith-Kline, Janssen Cilag, McNeil Pharma, MSD Sharp & Dohme and Pfizer to the
1080 University of Muenster (collection of sociodemographic and clinical data). Blood collection in the
1081 Dortmund Health Study was done through funds from the Institute of Epidemiology and Social
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1086 3. The FOCUS (Food chain plus) control sample is described in Muller, N., *et al.* IL-6 blockade by
1087 monoclonal antibodies inhibits apolipoprotein (a) expression and lipoprotein (a) synthesis in
1088 humans. *J Lipid Res* **56**, 1034-42 (2015). FOCUS was supported by the Federal Ministry of
1089 Education and Research BMBF (FKZ 0315540A). FOCUS is represented by Matthias Laudes¹
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1092 **The International Genomics of Alzheimer's Project (IGAP)**

1093 We thank the International Genomics of Alzheimer's Project (IGAP) for providing summary results
1094 data for these analyses. The investigators within IGAP contributed to the design and
1095 implementation of IGAP and/or provided data but did not participate in analysis or writing of this
1096 report. IGAP was made possible by the generous participation of the control subjects, the patients,
1097 and their families. The i-Select chips was funded by the French National Foundation on
1098 Alzheimer's disease and related disorders. EADI was supported by the LABEX (laboratory of
1099 excellence program investment for the future) DISTALZ grant, Inserm, Institut Pasteur de Lille,
1100 Université de Lille 2 and the Lille University Hospital. GERAD was supported by the Medical
1101 Research Council (Grant n° 503480), Alzheimer's Research UK (Grant n° 503176), the Wellcome
1102 Trust (Grant n° 082604/2/07/Z) and German Federal Ministry of Education and Research (BMBF):
1103 Competence Network Dementia (CND) grant n° 01GI0102, 01GI0711, 01GI0420. CHARGE was
1104 partly supported by the NIH/NIA grant R01 AG033193 and the NIA AG081220 and AGES
1105 contract N01-AG-12100, the NHLBI grant R01 HL105756, the Icelandic Heart Association, and
1106 the Erasmus Medical Center and Erasmus University. ADGC was supported by the NIH/NIA
1107 grants: U01 AG032984, U24 AG021886, U01 AG016976, and the Alzheimer's Association grant
1108 ADGC-10-196728.

1110 *Material and methods*

1111 International Genomics of Alzheimer's Project (IGAP) is a large two-stage study based upon
1112 genome-wide association studies (GWAS) on individuals of European ancestry. In stage 1, IGAP
1113 used genotyped and imputed data on 7,055,881 single nucleotide polymorphisms (SNPs) to meta-
1114 analyse four previously-published GWAS datasets consisting of 17,008 Alzheimer's disease cases
1115 and 37,154 controls (The European Alzheimer's disease Initiative – EADI the Alzheimer Disease
1116 Genetics Consortium – ADGC The Cohorts for Heart and Aging Research in Genomic
1117 Epidemiology consortium – CHARGE The Genetic and Environmental Risk in AD consortium –
1118 GERAD). In stage 2, 11,632 SNPs were genotyped and tested for association in an independent set
1119 of 8,572 Alzheimer's disease cases and 11,312 controls. Finally, a meta-analysis was performed
1120 combining results from stages 1 & 2.

1121

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1138 **Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC)**

1139 Data on glycaemic traits have been contributed by MAGIC investigators and have been downloaded
1140 from www.magicinvestigators.org. The investigators within MAGIC did not participate in the
1141 analysis, writing or interpretation of this paper.

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1272 The melanoma meta-analysis consortium was supported by CRUK Programme grants

1273 (C588/A19167 C8197/A10123, C8197/A10865), NIH grant (R01CA083115, RO1CA001833) NIH

1274 NCI (CA88363, CA83115, CA122838, CA87969, CA055075, CA100264, CA133996 and

1275 CA49449), the NHMRC (200071, 241944, 339462, 380385, 389927, 389875, 389891, 389892,

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 1464 The MESA and the MESA SHARe project are conducted and supported by the National Heart,
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 1466 is provided by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-
 1467 HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168,
 1468 N01-HC-95169, UL1-TR-001079, UL1-TR-000040, and DK063491. Funding for SHARe
 1469 genotyping was provided by NHLBI Contract N02-HL-64278. Genotyping was performed at

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1472 for the Lung CT dataset was provided by grants R01-HL077612 and RC1-HL100543.NIH
1473 Intramural award ZIAEY00403 supported the collection of eye-related data in MESA.

1474

1475 **The Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS)**

1476 We would like to thank the participants and staff of the Nurses' Health Study, the Health
1477 Professionals Follow-Up Study for their valuable contributions as well as the following state cancer
1478 registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD,
1479 MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The
1480 authors assume full responsibility for analyses and interpretation of these data. This work was
1481 supported by NIH R01 CA49449, P01 CA87969, UM1 CA186107, and UM1 CA167552.

1482

1483 **GWAS of non-alcoholic fatty liver disease (hepatic steatosis)**

1484 Bratati Kahali and Elizabeth K Speliotes were supported by the Doris Duke Medical Foundation,
1485 NIH grant R01DK106621-01, the University of Michigan Internal Medicine Department, Division
1486 of Gastroenterology, the University of Michigan Biological Sciences Scholars Program and The
1487 Central Society for Clinical Research.

1488

1489 **Pancreatic cancer case-control consortium (PanC4)**

1490 The Mayo Clinic Molecular Epidemiology of Pancreatic Cancer study was supported by the Mayo
1491 Clinic SPORE in Pancreatic Cancer (P50CA102701). The Yale University study was supported by
1492 grant number 5R01CA098870 from the NCI. The work at Johns Hopkins University was supported
1493 by NCI Grants P50CA62924 and R01CA97075 and the Lustgarten Foundation for Pancreatic
1494 Cancer Research. The Pancreas Tumor Registry at Memorial Sloan Kettering Cancer Center was
1495 supported by NIH P30CA008748 and the Goldstein Fund for Prevention, Control and Population

1496 Research. The work at MD Anderson was supported by NIH Grant R01CA98380. The UCSF
1497 study was supported in part by NCI Grants CA59706, CA108370, CA109767, CA89726, and
1498 CA98889 and by the Rombauer Pancreatic Cancer Research Fund. The University of Toronto
1499 study was supported by NIH Grant R01CA97075, the Lustgarten Foundation for Pancreatic Cancer
1500 Research, and the Ontario Cancer Research Network.

1501

1502 **Pancreatic Cancer Cohort Consortium (PanScan)**

1503 PanScan is the NCI cohort consortium genome-wide association study for pancreatic cancer. This
1504 research was supported by the Intramural Research Program of the National Institutes of Health,
1505 Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of
1506 Health, Department of Health and Human Services.

1507

1508 **The European Prospective Investigation into Cancer and Nutrition (EPIC) study**

1509 The coordination of EPIC is financially supported by the European Commission (DG-SANCO)
1510 and the International Agency for Research on Cancer. The national cohorts are supported by the
1511 Health Research Fund (FIS) of the Spanish Ministry of Health, Regional Governments of Andalucía,
1512 Asturias, Basque Country, Murcia (no.6236), Navarra and the Catalan Institute of Oncology, La
1513 Caixa (BM 06-130), Red Temática de Investigación Cooperativa en Cáncer (RD12/0036/0018;
1514 RD06/0020/0091; Spain); Danish Cancer Society (Denmark); Ligue contre le Cancer, Institut
1515 Gustave Roussy, Mutuelle Générale de l'Éducation Nationale, Institut National de la Santé et de la
1516 Recherche Médicale (INSERM; France); Deutsche Krebshilfe, Deutsches Krebsforschungszentrum
1517 (DKFZ) and Federal Ministry of Education and Research (Germany); the Hellenic Health
1518 Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro (AIRC) and National
1519 Research Council (Italy); Dutch Ministry of Public Health, Welfare, and Sports (VWS),
1520 Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON

(Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), and Statistics Netherlands (The Netherlands); Nordic Center of Excellence in Food, Nutrition, and Health Helga (Norway); Swedish Cancer Society, Swedish Scientific Council and Regional Government of Skane and Vasterbotten (Sweden); Cancer Research UK (C570/A16491, R.C. Travis; 14136, K.T. Khaw) and Medical Research Council (G1000143, K.T. Khaw; United Kingdom).

The PRACTICAL Consortium

(<http://practical.ccge.medschl.cam.ac.uk/>)

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1576

1577 *COGS acknowledgement and funding:*

1578 This study would not have been possible without the contributions of the following: Per Hall
1579 (COGS); Douglas F. Easton, Paul Pharoah, Kyriaki Michailidou, Manjeet K. Bolla, Qin Wang
1580 (BCAC), Andrew Berchuck (OCAC), Rosalind A. Eeles, Douglas F. Easton, Ali Amin Al Olama,
1581 Zsofia Kote-Jarai, Sara Benlloch (PRACTICAL), Georgia Chenevix-Trench, Antonis Antoniou,
1582 Lesley McGuffog, Fergus Couch and Ken Offit (CIMBA), Joe Dennis, Alison M. Dunning,
1583 Andrew Lee, and Ed Dicks, Craig Luccarini and the staff of the Centre for Genetic Epidemiology
1584 Laboratory, Javier Benitez, Anna Gonzalez-Neira and the staff of the CNIO genotyping unit,
1585 Jacques Simard and Daniel C. Tessier, Francois Bacot, Daniel Vincent, Sylvie LaBoissière and
1586 Frederic Robidoux and the staff of the McGill University and Génome Québec Innovation Centre,
1587 Stig E. Bojesen, Sune F. Nielsen, Borge G. Nordestgaard, and the staff of the Copenhagen DNA
1588 laboratory, and Julie M. Cunningham, Sharon A. Windebank, Christopher A. Hilker, Jeffrey Meyer
1589 and the staff of Mayo Clinic Genotyping Core Facility

1590

1591 Funding for the iCOGS infrastructure came from: the European Community's Seventh Framework
1592 Programme under grant agreement n° 223175 (HEALTH-F2-2009-223175) (COGS), Cancer
1593 Research UK (C1287/A10118, C1287/A 10710, C12292/A11174, C1281/A12014, C5047/A8384,
1594 C5047/A15007, C5047/A10692, C8197/A16565), the National Institutes of Health (CA128978)
1595 and Post-Cancer GWAS initiative (1U19 CA148537, 1U19 CA148065 and 1U19 CA148112 - the
1596 GAME-ON initiative), the Department of Defence (W81XWH-10-1-0341), the Canadian Institutes
1597 of Health Research (CIHR) for the CIHR Team in Familial Risks of Breast Cancer, Komen

1598 Foundation for the Cure, the Breast Cancer Research Foundation, and the Ovarian Cancer Research
1599 Fund.

1600

1601 **Sarcoidosis GWAS**

1602 This work was supported by the German Federal Ministry of Education and Research (BMBF)
1603 within the framework of the e:Med research and funding concept (SysInflame grant 01ZX1306A).
1604 This project received infrastructure support from the DFG Excellence Cluster No. 306
1605 “Inflammation at Interfaces”. Andre Franke receives an endowment professorship by the
1606 Foundation for Experimental Medicine (Zuerich, Switzerland).

1607

1608 **The Singapore Epidemiology of Eye Diseases Study (SEED)**

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1623 Singapore

1624

1625 **Acknowledgements of studies that contributed to the GWAS meta-analysis of telomere**
1626 **length⁴**

1627 *The Framingham Heart Study*

1628 The Framingham Heart Study is funded by National Institutes of Health contract N01-HC-25195.

1629 The Framingham GWAS component of this project was funded by the Division of Intramural

1630 Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD.

1631

1632 *TwinsUK*

1633 The study was funded by the Wellcome Trust; European Community's Seventh Framework

1634 Programme (FP7/2007-2013). The study also receives support from the National Institute for Health

1635 Research (NIHR) BioResource Clinical Research Facility and Biomedical Research Centre based at

1636 Guy's and St Thomas' NHS Foundation Trust and King's College London.

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